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IMPORTANCE OF THE BLOOD GROUPS IN LABORATORY AND CLINICAL MEDICINE*

FRED H. ALLEN, JR., M.D.†

BOSTON

"HUMAN beings have blood group patterns as distinctive and individual as fingerprints." This is a prediction that was first suggested by Landsteiner in 1927. He had just discovered the M-N blood groups and the P groups, and was then able with the use also of the A-B-O groups to subdivide human beings into 36 different types. At present it is possible, with the useful blood-typing serums so far discovered, to subdivide human beings into over 600,000 types. The commonest of these would be found once in 200 typings. Many of the uncommon types are so rare that one would not expect to find them once in a thousand years. Thus, Landsteiner's prediction is beginning to come true.

Table 1 presents most of the important blood factors that can now be identified by blood-typing tests. They comprise 9 independent "families" or "systems," the names of which are given in Column I. The Rh system is the largest and most complicated. The blood factors shown in Column II are of clinical importance — in blood transfusion and in pregnancy (D *is* "Rh" and what one ordinarily means when one *says* "Rh"). In at least 95 per cent of clinical difficulties resulting directly from the blood groups, A, B or Rh (D) (enclosed in the box) are involved, but any of the others may cause clinical problems. The blood factors shown in Column III rarely if ever cause transfusion reactions or erythroblastosis fetalis, but can be identified by typing tests.

It is very unlikely that the discovery of new blood groups will add significantly to the importance of blood grouping in clinical medicine, but such discoveries, which are sure to come, will vastly increase the already great importance of the blood groups in three other major fields — legal medicine, human genetics and anthropology.

The importance of the blood groups in legal medicine is obvious. Besides the identification of persons, the ability to determine that blood is *not* from a particular person is very important. Presently available typing serums allow exclusion to be demonstrated in 99.9 per cent of cases. The exclusion of paternity, when the man is falsely accused, is now possible in about 60 per cent of cases, and this record will improve with the discovery of new blood groups.

In the field of human genetics, the fact that the blood groups are the only normal characteristics of man that are really clear cut so far as their demonstration is concerned, and at the same time inherited by means of single dominant genes according to invariable rules, makes their value unique. At least 8 different chromosomes are "tagged" by blood-group genes.

The same characteristics make the blood groups of unique value in physical anthropology. The value of the blood groups in anthropology is further increased by the fact that they are not subject to variation because of environment or natural selection, as bone measurements, skin color and other physical features are. Data already collected show that various populations can be clearly distinguished by the characteristic frequencies of the various blood groups.

TABLE 1. *The Important Blood-Group Factors.*

I	II	III
A-B-O	A B	O
	D	
Rh	C c	
	E e	
M-N-S	M N	
	S s	
Kell	K k	
Duffy	Fy^a Fy^b	
Kidd	Jk^a	
P		P
Lewis		Le^a Le^b
Lutheran		Lu^a

*Presented at the annual meeting of the Massachusetts Medical Society, Boston, May 22, 1952.

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The Blood Groups in Transfusion Therapy

In the realm of clinical medicine, the importance of the blood-group factors is related directly to their antigenicity in human beings. A and B are presumably the strongest antigens of all the factors — at any rate, everyone who is "negative" to either of these factors quickly becomes sensitized, in infancy, so that all Group O persons, for example, have anti-A and anti-B. The A and B factors are therefore the most important ones in blood transfusion because there is no leeway for errors in typing or cross-matching, and the first error results in a hemolytic reaction that may be fatal. Next comes the Rh factor (D), which is also an effective antigen, usually sensitizing the "negative" person who is exposed to it through a blood transfusion. Sensitization itself has no harmful effect upon the person sensitized, but a second such transfusion results in a hemolytic reaction that may be fatal. Many K-negative persons can be sensitized to K (Kell) by transfusion of K-positive blood, and the same statement is true for E and c, but none of these are in the same class of importance with A, B and D. The other blood-group factors seem to be even less likely to cause sensitization, and are thus of distinctly minor clinical significance. Fatal transfusion reactions due to A, B or D are avoidable by accurate blood-typing tests. Fatal reactions due to K, E, c and the others are so uncommon that routine typing for these factors is not worth while. Two facts, however, are of great importance. The first is that over 80 per cent of all transfusions that are given are possible sensitizing transfusions, for one or more of the blood factors that may later be responsible for a fatal reaction. That is to say, no matter how accurate the typing tests, or how sensitive the cross-match test, over 80 per cent of bloods that are given contain one or more of these antigenic blood factors that the patient lacks and to which he may then become sensitized. The risk to the female patient is somewhat increased if the blood donor is her husband, since she presumably has had, or will later have, babies who have inherited his blood factors. The risk of sensitization to one of these blood factors, if the routine ABO and Rh tests are properly done, is not so great as to cause hesitation in the use of blood transfusions when lives are to be saved, but it is one of the main reasons for not giving a blood transfusion that is not really necessary.

Table 2. *Analysis of Hemolytic Transfusion Reaction.*

Cells of	Serum of Mrs. A.		
	Saline suspension	Albumin	Coombs test
Mrs. A.	—	—	—
Donor H. (reaction)	—	—	+
Donor G. (reaction)	—	—	+
Donor K. (no reaction)	—	—	—

The second important fact is that fatal hemolytic reactions caused by blood-group incompatibility are absolutely avoidable. For example, although it is not feasible to prevent *sensitization* to the Duffy factor Fy^a by typing test, since typing serum is not generally available, it is possible, if the patient does become sensitized, to pick compatible blood for future transfusions by using a sensitive cross-match test. In 23 per cent of all transfusions, Fy^a-positive blood is given to Fy^a-negative recipients. Table 2 shows what may happen. Mrs. A, a physician's wife, bled profusely after a spontaneous abortion. A transfusion was started but produced a reaction and had to be stopped. A second bottle of blood was tolerated well, but a third one caused another reaction. She and the three donors were all retyped and found to be all Group O, Rh+. The cross-match tests were repeated and seemed to indicate compatibility of all three donors. Samples were sent to the Blood Grouping Laboratory of Boston, and the typing tests were confirmed. The patient's serum was cross-matched with the red cells of the three donors, and with her own red cells as a control. In each case, the red-cell suspensions had been made in saline solution, which is the time-tried procedure, and there was no agglutination of any of the bloods, even after an hour's incubation. The saline solution was then replaced by 20 per cent bovine albumin, but again there was no agglutination. Up to this point, our findings were identical with the findings of the other laboratory. We went one step farther, however, and removed the albumin completely by washing the cells in saline solution and added to each tube a drop of Coombs serum. This time the cells of the two donors whose blood had caused reactions became strongly agglutinated, whereas the cells of the compatible donor, and the patient's own cells, remained unagglutinated. We could not identify the antibody in the patient's serum, though we recognized that it was different from any we had ever encountered, but were able to find compatible donors by using the Coombs test in the major cross-match, and she recovered with no further trouble. A month or two later, we were able to compare this serum with one sent us from London, and to identify the antibody as anti-Fy^a. Similar experiences could be told involving most of the other blood factors shown in Table 1. The important point is that the Coombs test, used in the cross-match, is an effective safeguard against the administration of incompatible blood to a patient who may have been sensitized to one of the blood-group factors by a previous transfusion or pregnancy, and this test should be used in such circumstances. Its effectiveness has been well demonstrated in several of the blood banks in Massachusetts, and it is now used routinely for all cross-matches in two of the largest hospitals in New York.

Erythroblastosis Fetalis

The practical problem of erythroblastosis fetalis, caused by Rh (D) incompatibility, has been crystallized by the discovery that the principal complication of this disease, the brain lesion known as

kernicterus, is preventable by proper treatment of the newborn baby. This complication formerly claimed over 15 per cent of erythroblastotic infants, and those who were not killed by it were permanently disabled with what is ordinarily indistinguishable from cerebral palsy. Prevention of kernicterus requires preparation in advance of the baby's birth. It is therefore necessary to know whether or not the pregnant woman is D negative and, if so, whether she has been sensitized to D. The blood typing and the test for sensitization can be done at the same time, preferably at about seven months' gestation — earlier, perhaps, if there is a history of erythroblastosis in a previous baby or of a blood transfusion that might have sensitized the mother. If no anti-Rh antibodies are found at seven months, the test should be repeated three or four weeks from term to ensure that the baby will not have erythroblastosis fetalis.

If sensitization to D is demonstrated, erythroblastosis should be expected in the baby, and complete preparation should be made in advance of its arrival, regardless of whether the maternal titer is high or low. Advance preparation for the baby means preparation for immediate exchange transfusion. Nothing else can be done before the birth of the infant, which is unfortunate because nearly a third of erythroblastotic babies are stillborn. We have not yet discovered any over-all advantage in delivering the babies before term that could counterbalance the greatly increased liability to brain damage in immature infants. In fact, up to the present time, the strict avoidance of immaturity has seemed to be one of the important preventive measures against kernicterus. Unfortunately, also, none of the measures that have been proposed for treatment of the mother have proved of any value, in spite of the enthusiasm of some of the early reports. On the other hand, there is impressive evidence that the majority of these babies are better off *in utero* than they are after separation from the placenta. When the baby is doing poorly *in utero*, nature not infrequently steps in with spontaneous premature labor. It has been our opinion for the past four and a half years that nature does a better job of deciding when these babies should be born than we could do.

When the babies are born, they are not jaundiced, and only a few of them have yellow vernix. A few, who have been doing poorly *in utero*, are desperately sick at birth, but most of them look like normal babies. Jaundice is the most important clinical feature, almost invariably appearing in the first twenty-four hours of life, except in the 15 to 20 per cent of erythroblastotic babies who never have trouble of any kind. (Jaundice appearing in the first twenty-four hours of life nearly always signifies erythroblastosis fetalis, regardless of whether the mother is Rh negative or Rh positive).

Jaundice rapidly increases during the first forty-eight hours of life, and its severity is directly related to the likelihood that the brain will be damaged, even though it is by no means certain that the bilirubin that makes the baby yellow is actually the agent that damages the brain. Exchange transfusion, used liberally, greatly lessens the severity of the jaundice, and prevents brain damage. The rational approach to the problem thus boils down to prenatal case finding by simple serologic tests done on the mother's blood during pregnancy, so that exchange transfusion can be done without delay after the baby is born.

To consider briefly the physiologic pathology, erythroblastosis is a disease caused by fetal-maternal blood-group incompatibility, the baby having one of the blood factors that its mother lacks, the mother producing antibodies (against that factor) that pass through the placenta into the baby's circulation, and the red cells of the baby being rapidly destroyed after contact with the antibody. That the rapid blood destruction does not usually kill the baby *in utero* is due to two important circumstances: the baby is usually able, by expansion of blood-forming activity in its liver and spleen, to make blood fast enough, though the equilibrium that is established between blood destruction and blood formation may be at a level of fairly severe anemia; and the circulation through the placenta usually removes the toxic by-products of red-cell destruction quite effectively.

Birth, which cuts off the introduction of further antibody, brings up two problems. Progressive anemia, consequent upon rapid decrease in the production of new red cells, is seldom difficult to recognize or deal with. Much more important is the inability of most newborn babies to excrete bilirubin, which piles up at a very rapid rate, and commonly reaches, within forty-eight hours, levels higher than are seen in any other clinical situation; serum bilirubin levels between 40 and 80 mg. per 100 cc. are not at all uncommon. Bilirubin, or something closely related to it in some way, is very damaging to the baby, and since he is usually unable to excrete it during the first forty-eight hours (even longer if he is premature), its production must be reduced if brain damage is to be avoided. We have shown that this is so, and several of the other large medical centers have arrived at similar conclusions. It has not been shown that ACTH or cortisone, or any other drug, is reliable in preventing the destruction of red blood cells. Exchange transfusion, however, by removing most of the circulating red cells of the baby and replacing them with red cells that are compatible with the maternal antibody, greatly reduces the formation of bilirubin. Even so, the bilirubin may rise to dangerous levels, in which case a second exchange transfusion is beneficial, not only by removing the baby's red cells that may have been released subsequent to the first transfusion but also by actually removing about a third of the total bilirubin. Reduction of the frequency of kernicterus

to practically 0 has been accomplished only since we began following an initial exchange transfusion with a second one in babies who became excessively jaundiced. Our present policy is to do serial tests of serum bilirubin, and to prevent it from ever exceeding 20 mg. per 100 cc. by repeated exchange transfusions if necessary. The technic of exchange transfusion, and the indications for it, have been thoroughly covered in a previous paper. Table 3 shows the results of progressive improvement in the care of these babies at the Boston Lying-in Hospital and Children's Hospital. In the first period, before exchange transfusion was used, and when half the births were induced before thirty-eight weeks, there were 42 cases per year, and 14, or a third, of the infants had kernicterus. In the second period, exchange transfusions were done in 73 per cent of the babies, but no attention was paid to the sex of the blood donor. During this period there were 82 erythroblastotic infants per year, but kernicterus occurred in only 8 (10 per cent). In the third period, 86 per cent of the babies were treated by exchange transfusion, 20 per cent had two or more exchange transfusions, blood from female donors was used almost exclusively, and only 25 per cent of the babies were born before thirty-eight weeks' gestation. Of 114 babies per year only 2 (less than 2 per cent) had kernicterus. This represents a large absolute decrease as well as a very large relative decrease in the frequency of kernicterus with improved treatment. One can be sure that a more conservative policy with respect to induction of labor played some part in this improvement. It is impossible to assess the value of the female donor blood per se, but there is absolutely no doubt about the effectiveness of multiple exchange transfusions.

TABLE 3. *Results in Erythroblastotic Infants Admitted Less than Twenty-four Hours after Birth.*

PERIOD	TOTAL CASES	RECOVERIES	INFANTS WITH KERNICTERUS	DEATHS (NOT KERNICTERUS)	CASES OF ERYTHROBLASTOSIS PER YEAR	CASES OF KERNICTERUS PER YEAR	EXCHANGE TRANSFUSIONS	MULTIPLE EXCHANGE TRANSFUSIONS	FEMALE DONORS	GESTATION OF LESS THAN 38 WK.
							%	%	%	%
Jan. '45 to Oct. '46	78	38 (49%)	26 (33%)	14 (18%)	42	14	0	—	—	50
Nov. '46 to Mar. '49	199	153 (77%)	20 (10%)	26 (13%)	82	8	73	0	16	47
Apr. '49 to June '51	257	225 (87%)	4 (2%)	28 (11%)	114	2	86	20	82	25

The diagnosis of erythroblastosis fetalis depends on what blood factor is causing the trouble in the particular case. In perhaps 80 per cent of cases it is the Rh factor (D). In such a case the mother is Rh negative, and routine prenatal testing will have demonstrated that she is one of the unlucky 5 per cent of Rh-negative women who become sensitized to Rh. Thus forewarned, the obstetrician collects a sample of umbilical-cord blood, on which the Coombs test is done. A positive Coombs test in a newborn baby always makes the diagnosis of erythroblastosis. Thus, diagnosis is no problem when the disease is caused by Rh. In about 20 per cent of the cases, when the disease is not caused by Rh, the mother is usually Rh positive; the obstetrician is not forewarned, and the infant almost always looks perfectly normal at birth. However, the baby becomes jaundiced during the first twelve to twenty-four hours of life, and the alert nurse reports it immediately. Blood is drawn from mother and baby, and both are blood typed, and the Coombs test is done on the baby. If the mother is Rh positive and the Coombs test of the baby's red cells is positive, the diagnosis is erythroblastosis of one of the uncommon group caused probably by Kell, E, or c. If, however, the Coombs test of the baby's red cells is negative and the baby is incompatible with the mother in the major blood groups, it is almost certain that it is one of that fairly large group of cases caused by major blood-group incompatibility. Table 4 shows the blood types of baby and mother that make erythroblastosis possible. This type of erythroblastosis is generally not predictable before birth. It is not known at present why the Coombs test is negative, and absolute diagnosis is difficult. However, two points can usually be demonstrated: serum bilirubin in the baby rising to 15 mg. per 100 cc. or higher during the first twenty-four hours, and an incompatible antibody in the baby's serum (anti-A or anti-B as the case may be). Both these findings are grossly abnormal. Another finding that is of some help is the almost invariable presence in the mother's serum of a very high titer of hyperimmune anti-A (or anti-B) antibody. This in itself is not diagnostic, because this type of antibody is found in many women whose babies are normal. Clinically, the infants with erythroblastosis caused by A-B-O incompatibility usually have a mild illness that re-

TABLE 4. *Incompatibilities That May Result in Erythroblastosis.*

GROUP OF BABY	GROUP OF MOTHER
A	O
B	O
A or AB	B
B or AB	A

quires no treatment. Severe jaundice, with very high serum bilirubin levels, and brain damage are not uncommon, however, and these babies should be given exchange transfusions if necessary to keep the serum bilirubin below about 20 mg. per 100 cc.

One further point about treatment concerns erythroblastotic infants who are very sick at birth and who frequently appear to be in congestive heart failure at the time treatment is started. The great advantage of exchange transfusion is never more striking than in these cases, in which the simple removal of more blood than is put in frequently results in dramatic improvement. Exchange transfusion is the only method whereby the blood volume can be reduced simultaneously with the correction of anemia.

Summary

Over 80 per cent of transfusions are potentially dangerous because of the possibility of sensitizing the recipient to E, c, Kell, Duffy, S or one of the other antigenic blood-group factors. Husbands are undesirable donors for their wives if other donors are available. Hemolytic blood-transfusion reactions are avoidable by the use of the Coombs test for the cross-match.

Erythroblastosis fetalis occurs not infrequently in the babies of Rh-positive women. In these cases A and B are much more frequently involved than E, c and Kell, and other blood factors are but rare causes. Jaundice is *not* present at birth. Jaundice in the first twenty-four hours of life is always abnormal, and usually means erythroblastosis fetalis.

Effective treatment of erythroblastosis fetalis requires prenatal testing of pregnant women, observation of jaundice in all newborn babies, and close co-operation among obstetrician, pediatrician, nursing staff and blood bank.

Brain damage is related to severe jaundice and high serum bilirubin. Kernicterus, as well as severe jaundice, can be prevented by exchange transfusion. Early exchange transfusion is much more effective than delayed exchange transfusion in preventing severe jaundice and kernicterus. Exchange transfusion should be repeated in babies who show increasingly severe jaundice.

THE CLINICAL USE OF NOR-EPINEPHRINE IN THE TREATMENT OF SHOCK ACCOMPANYING MYOCARDIAL INFARCTION AND OTHER CONDITIONS*

George S. Kurland, M.D.,† and Monte Malach, M.D.‡

BOSTON

THE recent availability of pure L-nor-epinephrine (arterenol, nor-adrenaline) has permitted evaluation of its clinical usefulness as a pressor agent. Preliminary reports[1-7] have suggested beneficial results after its use in the treatment of peripheral vascular collapse. The purpose of this paper is to describe our experience with the drug, particularly in the successful treatment of shock accompanying acute myocardial infarction.

Pharmacologic Properties

Nor-epinephrine (aminoethanol catechol) is a sympathomimetic primary amine, first synthesized by Stoltz[8] in 1904. It can be distinguished from epinephrine by chemical, chromatographic and physiologic methods.[9] The formulas are shown in Figure 1. Naturally occurring nor-epinephrine has been identified as the levo isomer; subsequent mention refers to this compound. Nor-epinephrine has been found in blood, urine and adrenal medulla,[10] tissues containing adrenergic nerve fibers and in large amounts in some tumors of the adrenal medulla.[11] It has not been detected in bone marrow or placenta.[9] It is present in *USP* epinephrine in concentrations[10, 12] varying up to 36 per cent.

Effects on Cardiovascular System

The effects of epinephrine and nor-epinephrine on the cardiovascular system have recently been reviewed.[13, 14] Nor-epinephrine produces a generalized arterial, capillary and venous vasoconstriction, with an increase in total peripheral resistance and a resultant increase in systolic, diastolic and mean

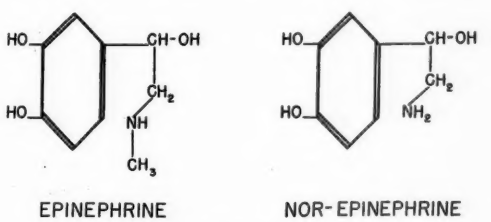

FIGURE 1. *Structural Formulas of Epinephrine and Nor-epinephrine.*

*From the Medical Research Department, Yamins Research Laboratory, Beth Israel Hospital, and the Department of Medicine, Harvard Medical School.

Aided by a grant from the William F. Milton Fund, Harvard Medical School.

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systemic arterial blood pressures. The cardiac output is decreased. It also causes an increase in mean arterial, capillary and venous pressure in the pulmonary circuit. Nor-epinephrine decreases pulse rate in the normotensive human being and in the intact animal; atropine abolishes the bradycardia. The effect on blood flow in the skin is variable. Muscle blood flow is decreased during intra-arterial

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TABLE 1. *Clinical Effects of Nor-Epinephrine.*

Case No.	Sex	Initials	Age	Diagnosis	Congestive Heart Failure	Pulmonary Edema
			yr.			
1A	F	B. B.	58	Acute myocardial infarction	Present	Absent
1B	F	B. B.	58	Acute myocardial infarction	Present	Present
2	F	R. P.	72	Acute myocardial infarction; hypertensive heart disease; paroxysmal auricular fibrillation.	Present	Present
3	F	J. P.	70	Acute myocardial infarction; rheumatoid arthritis.	Present	Present
4	F	E. B.	70	Acute myocardial infarction; low-salt syndrome.	Present	Present
5	M	I. K.	58	Acute myocardial infarction; chronic glomerulonephritis; uremia; hypertensive heart disease.	Present	Absent
6	M	B. F.	58	Acute myocardial infarction; diabétes mellitus; hypertensive heart disease.	Present	Present
7	M	R. S.	76	Acute myocardial infarction	Present	Present
8	M	P. K.	55	Acute myocardial infarction; hypertensive heart disease.	Absent	Absent
9	F	J. P.	66	Acute myocardial infarction; hypertensive heart disease; diabetes mellitus; low-salt syndrome.	Present	Absent
10	M	E. F.	57	Acute myocardial infarction; duodenal ulcer; cystitis.	Present	Absent
11	M	G. S.	62	Acute myocardial infarction	Absent	Absent
12	M	M. S.	60	Acute myocardial infarction; hypertensive heart disease; cerebrovascular disease.	Absent	Absent
13	M	J. P.	57	Acute myocardial infarction; bleeding duodenal ulcer; carcinoma of cecum; abdominal carcinomatosis.	Absent	Absent
14	F	A. B.	75	Acute myocardial infarction; pulmonary embolism; adenocarcinoma of rectum (abdominoperineal resection).	Absent	Absent
15	F	S. T.	78	Pulmonary emboli; hypertensive heart disease; auricular fibrillation.	Present	Present
16	M	P. M.	70	Mesenteric thrombosis; peritonitis.	Absent	Absent
17	M	E. S.	65	Embolism of superior mesenteric lymph nodes; hypertensive heart disease; auricular fibrillation.	Absent	Absent
18	M	A. D.	72	Infarction of omentum; strangulated hernia; carcinoma of esophagus; arteriosclerotic heart disease.	Present	Absent
19	M	F. O.	37	Gastrointestinal hemorrhage; ulcerative ileocolitis; low-salt syndrome.	Absent	Absent
20	M	J. O.	77	Quinidine shock; pulmonary fibrosis; interstitial myocarditis; carcinoma of prostate.	?	Absent
21	F	F. M.	73	Cholangitis; sepsis.	Absent	Absent
22	M	S. J.	68	Pyelonephritis; sepsis; low-salt syndrome.	Absent	Absent
23	F	L. C.	54	Peritonitis; pulmonary embolism; sigmoid carcinoma; diabetes mellitus; hypertension.	Absent	Absent
24	F	A. D.	67	Peritonitis; ulcerative colitis; diverticulitis (sigmoid resection).	Absent	Absent
25	M	A. M.	68	Carcinoma of pancreas (gastrojejunostomy and cholecystojejunostomy)	Absent	Absent
26	M	H. S.	60	Enterocolitis; bleeding peptic ulcer (subtotal gastrectomy); hypertension.	Absent	Absent
27	M	S. Z.	60	Perforated duodenal ulcer; peritonitis; rheumatic heart disease; mitral stenosis; aortic stenosis and insufficiency.	Present	Absent
28	F	D. S.	51	Carcinoma of adrenal cortex; hypertensive heart disease; duodenal ulcer; old myocardial infarction.	Present	Present
29	M	A. B.	62	Barbiturate intoxication; involutional melancholia.	Absent	Absent
30	F	L. R.	55	Peritonitis; carcinoma of ovary; abdominal carcinomatosis.	Present	Present

infusion of nor-epinephrine, but is not changed during intravenous administration. Splanchnic blood flow,[15] as measured by hepatic clearance, is not changed significantly. Nor-epinephrine produces a decrease in renal plasma flow[16] and a rise in the filtration fraction owing to efferent glomerular arteriolar constriction. The drug[17] causes a marked increase in cerebrovascular resistance and a de-

TABLE 1. (*Concluded*).

CASE NO.	PREVIOUS THERAPY	DURATION OF NOR-EPINEPHRINE THERAPY	BLOOD PRESSURE		ADDITIONAL THERAPY	PHLEBITIS OR SKIN ULCERS
			BEFORE TREATMENT	AFTER TREATMENT		
1A	Paradrine and plasma	a. 45 min. b. 36 hr.	80/70 80/60	120/82 110/80	Cortisone	Present Present
1B	Paredrine and plasma	a. 36 hr. b. terminally	70 systolic 0/0	110 systolic 0/0	Penicillin and aureomycin	Present
2	Paredrine	10 hr.	0/0	115/70	.....	Absent
3	Paredrine and plasma	Terminally	0/0	0/0	.....	Absent
4	.....	16 hr.	40/0	130/80	.....	Present
5	Paredrine	16 hr.	60 systolic	140 systolic	.....	Present
6	Paredrine, caffeine and epinephrine	10 min.	80/60	0/0	.....	Absent
7	.....	1 hr.	0/0	0/0	.....	Absent
8	.....	1½ hr.	90 systolic	128 systolic	.....	Absent
9	Whole blood	6 days	60 systolic	105 systolic	.....	Present
10	.....	12 hr.	75/60	110/70	.....	Absent
11	.....	10 hr.	0/0	120/80	.....	Absent
12	Plasma	5 days	0/0	120/80	.....	Present
13	Whole blood	30 min.	0/0	0/0	.....	Absent
14	Whole blood, plasma and Neo-synephrine	20 hr.	60/40	90/60	Aureomycin	Absent
15	Paredrine and polyvinyl pyrrolidone	30 min.	0/0	0/0	.....	Absent
16	Whole blood and paredrine	a. 3 hr. b. 6 hr. c. 21 hr. d. 12 hr.	70/0 84/50 50/0 70/50	90/60 120/70 90/60 100/60	Aureomycin, penicillin and streptomycin	Present
17	.....	8 hr.	110/70	130/80	.....	Absent
18	Whole blood and Neo-synephrine	10 hr.	80/60	100/80	Aureomycin and penicillin	Present
19	Whole blood	12 hr.	0/0	96/70	Penicillin	Present
20	Paredrine, caffeine and epinephrine	3 hr.	60/30	100/50	.....	Absent
21	Paredrine, whole blood and plasma	2 days	60/40	108/80	Aureomycin and chloromycetin	Present
22	Whole blood and adrenal extract	a. 5 days b. terminally	0/0 0/0	100/60 0/0	Streptomycin, penicillin, Gantrisin and intra-arterial blood	Present Absent
23	.....	7 hr.	80 systolic	120 systolic	Aureomycin	Present
24	Whole blood, cortisone and aqueous adrenocortical extract	12 hr.	70/50	90/60	Aureomycin	Present
25	Neo-synephrine, whole blood and ACTH	13 hr.	50/0	80/60	Aureomycin	Absent
26	Whole blood and plasma	6 hr. terminally	90/60	110/80	Aureomycin and penicillin	Present
27	Plasma	30 hr.	80/50	100/60	Aureomycin and penicillin	Absent
28	Whole blood (intravenously and intra-arterially), plasma ACTH and cortisone	36 hr.	110/80	110/80	Chloromycetin	Absent
29	Intracardiac administration of epinephrine	2 days	0/0	120/80	Benzedrine, coramine, penicillin, streptomycin and Chloromycetin	Present
30	Cortisone, whole blood and epinephrine	12 hr.	0/0	100/70	Aureomycin	Absent

crease in cerebral blood flow, without significant alteration in cerebral oxygen consumption.

In contrast, in the normotensive human being, epinephrine increases the systolic blood pressure and the mean systemic arterial pressure, but has a variable effect on the diastolic blood pressure. The total peripheral resistance is decreased. Its administration results in an increase in cardiac output and pulse rate. Although epinephrine decreases skin blood flow by cutaneous vasoconstriction, blood flow to the muscles and splanchnic area[15] is increased. It constricts efferent glomerular arterioles,[16] decreases renal plasma flow and increases the glomerular filtration fraction.

Other Effects

Nor-epinephrine has neither the calorigenic effects of epinephrine nor its hyperglycemic action. Striking rises in oxygen tension in areas of myocardial ischemia have been demonstrated[18] after the intravenous administration of nor-epinephrine (0.5 microgm. per kilogram of body weight) but not after epinephrine. Anxiety, restlessness and apprehension, produced by epinephrine, do not occur with nor-epinephrine.

Material and Results

Thirty patients, 18 males and 12 females, whose ages varied from thirty-seven to seventy-eight years were treated with 37 infusions of nor-epinephrine. In 14, treatment was instituted because of the existence of shock accompanying acute myocardial infarction; in the other 16 patients shock was associated with hemorrhage, pulmonary embolism, embolism of the superior mesenteric artery, generalized sepsis, barbiturate intoxication, the administration of quinidine or pronestyl, peritonitis and resection of an adrenocortical carcinoma.

All patients exhibited the clinical manifestations of profound shock, including a precipitous fall in blood pressure, cold extremities, moist, clammy skin, ashen-gray pallor and a rapid or imperceptible radial pulse. Loss of consciousness was noted in 18 patients. In 23 patients previous treatment had included intravenous administration of plasma, whole blood, paredrine, Neo-synephrine, epinephrine, cortisone, ACTH or aqueous adrenocortical extract. Two patients (Cases 25 and 26) in whom nor-epinephrine was ineffective were subsequently treated with an artificial kidney to raise the blood pressure, without success. Eight hundred cubic centimeters of whole blood was administered intra-arterially in Case 22 after nor-epinephrine had failed to produce a pressor response. It was temporarily effective.

Dose and Duration of Treatment

Nor-epinephrine, supplied in ampoules containing 4 mg. of the bitartrate monohydrate,* was diluted in 1000 cc. of 5 per cent glucose or 0.85 per cent sodium chloride to yield a solution for intravenous administration containing 4 microgm. per cubic centimeter.

The flow of nor-epinephrine was maintained at a rate sufficient to elevate the systolic blood pressure to approximately 100 or to alleviate the clinical manifestations of shock. A pressor effect, noted several minutes after an effective infusion rate, was observed in 30 of 37 courses of treatment.

The average maintenance rate was 20 to 30 drops per minute. A Murphy-drip apparatus, controlled by a simple tunnel clamp, frequently observed, was adequate to maintain a satisfactory rate of flow and stable blood pressure. Wide variations and persistently high levels of systolic blood pressure were avoided.

Treatment was continued for ten minutes to six days. Abrupt cessation of nor-epinephrine often resulted in a sudden drop of blood pressure. Accordingly, the rate of flow was gradually decreased four to six hours after the blood pressure had become stabilized; an intravenous infusion of 5 per cent glucose in water was continued for an additional twelve to twenty-four hours to facilitate emergency therapy if needed. In 8 patients cessation of nor-epinephrine resulted in a drop of the systolic blood pressure to 80 or below and a return of the clinical manifestations of shock. Each of these 8 patients exhibited a good response to immediate reinstitution of nor-epinephrine therapy. Three patients recovered from an initial episode of peripheral vascular collapse but required additional nor-epinephrine six hours to eight weeks later (Cases 1, 16 and 22) because of a subsequent episode of shock. One patient (Case 16) responded to nor-epinephrine on four occasions. The largest amount administered to a single patient (Case 22) was 62 mg. during five days.

The clinical effects of 37 infusions of nor-epinephrine in 30 patients are summarized in Table 1. The results are separated into those obtained in patients with myocardial infarction and those obtained in patients with shock associated with other conditions.

Results in Acute Myocardial Infarction

A significant pressor response was observed in 12 of 17 courses of treatment in 14 patients with shock accompanying acute myocardial infarction. Four of these patients ultimately survived; 5 died one to forty-one days after recovery from the initial episode of collapse.

Congestive heart failure accompanied the acute myocardial infarction in 9 of the 14 cases; a pressor response was obtained in 6 of the 9 patients. Acute pulmonary edema was observed in 6 patients, in 3 of whom a pressor response was recorded. Aggravation of congestive failure or pulmonary edema was not observed. One patient (Case 5) had suffered a

*Levophed, supplied through the courtesy of Mr. Sheppard M. Crane, Winthrop-Stearns, Inc., New York City.

twelve-hour episode of pulmonary edema three days prior to the development of peripheral vascular collapse. A significant pressor response was observed without reprecipitation of acute pulmonary edema. In 1 patient (Case 1B) acute pulmonary edema developed immediately after the administration of nor-epinephrine; the pulmonary edema responded to treatment with morphine, aminophylline and atropine during continued nor-epinephrine therapy.

The following case illustrates the effect of nor-epinephrine on acute myocardial infarction.

Case 12 (B. I. H. M28750). A 60-year-old man with a past history of hypertension, cerebrovascular accident, intermittent claudication and previous myocardial infarct was admitted to the hospital for the 4th time because of increasing angina pectoris of 7 days' duration culminating in an episode of severe substernal chest pain, followed by collapse and loss of consciousness. He was cyanotic and pulseless and was bathed in cold perspiration; the blood pressure could not be obtained. The chest was emphysematous; the lungs were clear. The heart was slightly enlarged; heart sounds were inaudible. An electrocardiogram revealed the pattern of an acute posterior myocardial infarction.

An intravenous infusion of nor-epinephrine, 4 microgm. per cubic centimeter, was started at a rate of 40 to 50 drops per minute (Fig. 2). There was an immediate rise in the systolic blood pressure to 70 and a further gradual rise to 120/80 during the following 5 minutes. The skin became warmer; evidence of collapse disappeared. The infusion was continued for 5 days at 20 to 30 drops per minute. Each attempt to slow the rate of infusion during this period resulted in a drop of systolic blood pressure to 80 to 90 and a return of the clinical manifestations of shock.

Twenty-four hours after the nor-epinephrine infusion had been started, streaky red phlebitis and blue-white discoloration along the vein occurred, resulting in superficial skin ulceration 48 hours later. This was observed with each infusion. Hot packs above the needle site minimized the venospasm, and the lesions healed uneventfully.

On the 6th day, nor-epinephrine was omitted, and the blood pressure remained at 120/80. Convalescence from the myocardial infarction was uneventful.

Results in Shock Due to Miscellaneous Conditions

A significant pressor response was observed in 18 of 20 courses of treatment in 16 patients with shock from other causes such as peritonitis, embolic disease and sepsis. Although a good pressor response to nor-epinephrine was obtained in most of these cases, only 3 patients ultimately survived. This is testimony to the serious nature of the underlying diseases.

The use of nor-epinephrine in noncardiac collapse is illustrated in Case 29 (B. I. H. M29062), a sixty-two-year-old man admitted to the hospital comatose after a self-administered overdose of barbiturates. Coramine, Benzedrine, positive-pressure oxygen and artificial respiration were given. Intracardiac administration of epinephrine was utilized during two episodes of cardiac standstill. The blood pressure, initially 100 systolic, 60 diastolic, became unobtainable twelve hours later; clinical signs of peripheral vascular collapse were present. The infusion of nor-epinephrine, 4 microgm. per cubic centimeter, was followed by a rise in the blood pressure to 110 systolic, 80 diastolic, and disappearance of the manifestations of shock. Attempts to terminate the infusion during the following two days resulted in a drop of the blood pressure. Thereafter the patient made an uneventful recovery.

Complications

Intense venospasm and ulceration of the skin have previously been reported[19] after the intravenous administration of nor-epinephrine. We have also noted in 14 of 30 cases local venospasm, pallor, cold skin and cyanosis in the area of insertion of the needle within one to twenty-four hours of the start of the infusion. Subsequently, a red, streaky phlebitis surrounded the area. A vesicular eruption or

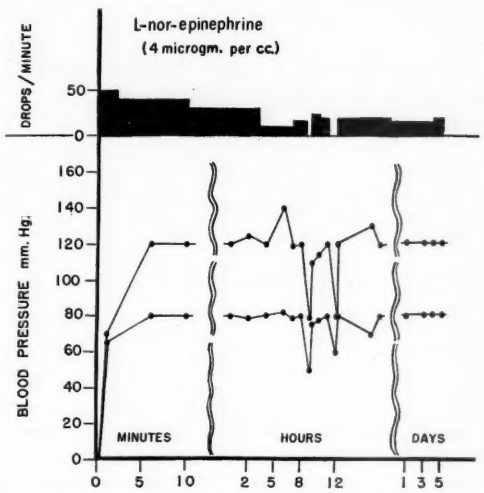

Figure 2. *Response of the Blood Pressure to the Intravenous Infusion of Nor-epinephrine in Shock Accompanying Acute Myocardial Infarction (Case 12).*

superficial ulcerations were noted in some cases; in all these cases complete healing occurred.

A deep skin ulcer was observed in a case in which there had been no obvious extravascular leakage of nor-epinephrine. A seventy-three-year-old woman (Case 21) was in peripheral vascular collapse accompanying cholangitis and generalized sepsis; the blood pressure was 60 systolic, 40 diastolic, and the pulse rate 140. A polyethylene catheter was inserted at the ankle and extended intravenously to the midportion of the leg. Nor-epinephrine (4 microgm. per cubic centimeter) and aureomycin (1 mg. per cubic centimeter) were administered through the catheter. The blood pressure rose to 108 systolic, 80 diastolic, and the pulse fell to 86. The infusion was continued for two days. A blue-white discoloration was noted at the tip of the catheter and continuing along the course of the vein; this was followed by a deep, penetrating, sec-

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ondarily infected ulcer. Complete healing followed débridement and multiple skin grafts.

Extravascular infiltration of nor-epinephrine may result in intense vasospasm, with subsequent necrosis and ulceration of the skin. This complication has not been noted after administration in the muscular arm region but has consistently followed extravascular infiltration in the skin of the hand and foot. Intravenous infusions of nor-epinephrine in the leg are to be administered with caution in the presence of peripheral vascular disease or diabetes mellitus. The application of hot packs at and above the level of the needle has decreased the incidence and severity of cutaneous reactions.

No arrhythmias that could be attributed to nor-epinephrine were noted.

Discussion

The evaluation of an agent in the treatment of the peripheral vascular collapse following myocardial infarction is difficult. The prognosis in many cases is ominous, and recovery has been regarded as uncommon[20] if the systolic blood pressure remains persistently below 80, particularly if the pulse pressure is low. In some patients death has occurred despite all therapy. On the other hand, many patients undergo a period of mild or transient shock and recover without specific treatment.[21]

The use of a pressor agent to treat the shock accompanying myocardial infarction is a relatively new concept.[22-25] Pressor agents have previously been said to be contraindicated in all forms of shock because maximal arteriolar constriction was already present; it was feared that further vasoconstriction would increase capillary anoxia and aggravate shock. Peripheral vascular collapse following coronary occlusion has been regarded as a compensatory phenomenon that decreased the work of heart. Prolonged profound shock, however, must be vigorously combated. The deleterious effects of shock on heart muscle[26] and the occurrence of multiple fresh coronary occlusions[27] in patients with antecedent shock emphasize the importance of successful alleviation of peripheral vascular collapse in patients with acute myocardial infarction. Intravenous injection of plasma, intravenous and intra-arterial administration of whole blood, epinephrine, paredrine, Neo-synephrine and methoxamine have been suggested[28-30] for their pressor effect. Various factors, including increased blood volume and cardiac work, myocardial irritability, central-nervous-system stimulation and the rapid development of tachyphylaxis, have limited the usefulness of these agents.

Preliminary observations in the literature and our findings suggest the beneficial effect of nor-epinephrine as a pressor agent. The pressor effect of nor-epinephrine is not attended by increased heart rate, cardiac output or central-nervous-system stimulation. We have not observed the development of tachyphylaxis. In Case 16, the administration of nor-epinephrine was followed by a satisfactory pressor response on four occasions. Of possible significance in patients with myocardial infarction is the observation of coronary-artery vasodilation[31] after nor-epinephrine. The effectiveness of this agent in our series is particularly striking since a pressor response was obtained in many patients who had previously failed to respond to other therapy, including oxygen, shock blocks, plasma, whole blood, paredrine, Neo-synephrine and epinephrine. No patient survived in whom shock was refractory to nor-epinephrine.

It is recognized that, in the use of nor-epinephrine to combat the shock accompanying acute myocardial infarction, treatment is directed at only one consequence of the underlying pathologic condition. However, it is our impression that in correcting the state of shock we have enabled certain patients (such as Case 12) to recover from the initial episode, which otherwise gave every indication of culminating in death. It is believed that through the use of this agent, the mortality in acute myocardial infarction may be, to a limited extent, decreased. Many of the patients who responded to nor-epinephrine ultimately died despite restoration of a satisfactory blood pressure and recovery from the clinical manifestations of peripheral vascular collapse. This is to be anticipated since shock occurs, generally, in the more seriously ill patients. It is to be noted that many of the deaths occurred suddenly, one to forty-one days after administration of nor-epinephrine, and without relation to the initial episode of shock.

The increase in arterial, capillary and venous pressures in the pulmonary circuit following the administration of nor-epinephrine to normotensive human beings[13] raised the possibility of aggravation or production of congestive heart failure or pulmonary edema after its use in patients with myocardial infarction. Our experience is illuminating in this regard, suggesting that nor-epinephrine may be used with caution in patients who have congestive heart failure, pulmonary edema or mitral stenosis. In 1 patient (Case 1B) pulmonary edema developed immediately after the administration of nor-epinephrine; the pulmonary edema cleared despite further nor-epinephrine. In 2 other patients (Cases 2 and 4) clearing of existing pulmonary edema continued despite the administration of nor-epinephrine. Three patients died without change in pulmonary edema; none of them had exhibited a pressor response to nor-epinephrine (Cases 3, 6 and 7). No increase in cardiac decompensation occurred in patients who were treated for shock and also suffered from congestive heart failure; 1 of these had mitral stenosis (Case 27).

Nor-epinephrine has previously been successfully utilized in the therapy of shock associated with a variety of pathologic states.[1-6] In our series, also,

nor-epinephrine achieved striking pressor responses in patients suffering from shock that accompanied conditions other than acute myocardial infarction.

The pressor effect of nor-epinephrine has been potentiated experimentally by desoxycorticosterone acetate,[32] tetraethylammonium bromide,[33] adrenocorticotrophic hormone[34] and cortisone.[34] Our data are insufficient to permit any conclusions concerning the clinical effectiveness of these agents in conjunction with nor-epinephrine in the treatment of shock.

Summary

Nor-epinephrine (aminothanol catechol) has been utilized as a pressor agent during 37 episodes of shock in 30 patients. A solution of the bitartrate monohydrate containing 4 microgm. per cubic centimeter was infused intravenously with a Murphy-drip apparatus at a rate (usually 20 to 30 drops per minute) sufficient to elevate the systolic blood pressure to 100 or to alleviate the manifestations of shock. Infusion was continued until the patient was able to maintain adequate blood pressure without therapy. The longest duration of treatment was six days; the largest amount administered was 62 mg.

In 14 patients who suffered vascular collapse with an acute myocardial infarction, a satisfactory pressor response was observed in 12 of 17 courses of treatment.

In 16 patients with shock accompanying various other pathologic states, a satisfactory pressor response was observed in 18 of 20 courses of treatment.

The only complication of nor-epinephrine therapy observed was intense venospasm, phlebitis and skin ulceration in 14 patients. This complication was decreased by the use of hot packs above the needle site. Complete healing occurred in all cases.

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PULMONARY FUNCTION IN CONVALESCENT POLIOMYELITIC PATIENTS*

III. Compliance of the Lungs and Thorax

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WHEN function of the muscles of respiration is impaired by poliomyelitis, one of the primary problems in convalescence is the disturbance of the mechanics of respiration, caused in part by atrophic and fibrotic changes in thoracic structures. While the patient is being treated in a mechanical respirator a diminution of thoracic or pulmonary distensibility, or both, can be overcome by use of adequate pressure fluctuations in the respirator. However, such alterations in distensibility, when present, constitute a major handicap to a patient attempting to ventilate his lungs by his own muscular power.

A previous report[1] has indicated that the resting end-expiratory position (functional residual volume) is within normal limits in poliomyelitic patients with varying degrees of respiratory-muscle paralysis and in various stages of convalescence. This means that emphysema in the true sense has not occurred, nor has there been any collapse of the chest. Additional studies[2] of the pressure-volume relations in chronic respirator patients have shown that the thorax and lungs combined are less easily distensible (or less compliant) than in normal persons. In the initial studies it was not possible to determine whether this change was due to an alteration in the compliance of the lung, or of the thorax, or of both. The present investigation was undertaken to determine which portions of the respiratory system were involved and to what extent.

A change in the distensibility of the lungs and thorax could result from alterations in viscous or in elastic properties of the structures or in both. An example of the former would be increased frictional resistance to deformation resulting from either constriction of the air passages or increased viscosity of tissue constituents. These changes may be separated from alterations in the elastic properties of the lungs and thoracic wall since viscous behavior is apparent only while the respiratory structures are in the process of being deformed. When the system is static, as at the transition points between the phases of respiration, no volume change is taking place and the pressures acting at these points in time are elastic pressures. When changes in elastic pressure during one phase of the respiratory cycle are related to the lung-volume change that has taken place, a measure of the elastic properties of the system is afforded. If, in 2 subjects, the same volume of inspiration is accompanied by twice as much elastic-pressure change in 1 person as compared to the other, it is apparent that, in terms of the elastic properties of the respiratory system, 1 is half as easily distensible as the other. In quantitating this type of change we have chosen to express the volume-pressure relation as the volume change in liters per centimeter of water elastic-pressure change, which expresses the compliance of the system. This usage of the term compliance is consistent with accepted engineering terminology.

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METHODS

Seven patients (4 female and 3 male) who were convalescing from respiratory-muscle paralysis due to poliomyelitis and who needed respiratory assistance for more than 50 per cent of the time were studied. The time since the onset of illness varied from three to sixteen months, and the interval that they could be without mechanical respiratory aids varied from three minutes to ten hours. Their vital capacities varied from 240 to 1400 cc. Chest x-ray films of these patients in the recumbent anteroposterior position showed no evident pulmonary disease. Normal values for respiratory compliance were obtained from 2 relaxed, trained male subjects who were completely familiar with the procedure and the apparatus.

Pressures were measured in the tank respirator, at the patient's mouth and in the esophagus. The intra-esophageal pressure was utilized as a measure of interpleural pressure variation. It should be pointed out that this represents a sample of interpleural pressure variation at one point within the thorax. In our analysis of lung compliance the assumption is made that this sample approximates the mean of interpleural pressure variation at all points on the surface of the lungs. Experimental evidence supporting this assumption, within the limits of the measurements reported here, has been obtained in animals. Consistency of human lung compliance values, obtained with the technic described, with the results obtained by other methods further substantiates this assumption.[3]

Intra-esophageal pressures were obtained by means of a small (2-cc. capacity) balloon on a 63.5-cm. length of polyethylene tubing (1.5 mm. in diameter) passed through the nose and into the esophagus to a depth of 43 cm. from the nose. Pressures in the balloon were recorded at its relaxation volume, so that the pressure-volume characteristics of the balloon did not interfere with the measurement. The system was air filled.

The pressure difference across the lungs or thorax, or both together, was desired. This was obtained with the use of a differential mechanoelectric pressure transducer so constructed that, for example, the pressure at the mouth could be conducted to one side of the diaphragm and the tank pressure to the other side. The pressure recorded was then the pressure difference across the lungs and thorax. The voltage output from the mechanoelectric pressure transducer (inductance type) was linear with pressure in the range employed, and the transducer had adequate frequency-response characteristics and sensitivity. The output was amplified and recorded on one channel of a multichannel, direct-writing oscillograph (Poly-viso*). This pressure difference was also plotted on the horizontal axis of a cathode-ray oscilloscope.[4]

The air flow into and out of the lungs was measured by means of a low-resistance monel screen calibrated for flow in the desired range[5] and a mechanoelectric transducer similar to the one described above but of higher sensitivity. The voltage-output changes, which were linear with flow, were amplified and recorded on a second channel of the multichannel, direct-writing oscillograph. The air-flow rate was electrically integrated so that the volume could be recorded on a third channel of the recorder and on the vertical axis of the cathode-ray oscilloscope.[4]

*Sanborn Company, Cambridge, Massachusetts.

The use of the oscilloscope permitted simultaneous plotting of the pressure difference across the lungs (mouth to esophagus) or the lungs and thorax (mouth to body surface inside the respirator) against the volume of air moved. With each respiration a closed loop was produced on the oscilloscope face.

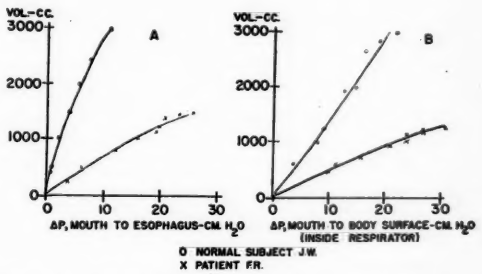

FIGURE 1. *Typical Compliance Plots of Lungs* (A) *and Lungs and Thorax* (B).

The points of no air flow at the end of inspiration and the end of expiration occurred at the volume extremes of these loops. These points were plotted from the oscilloscope face on co-ordinate paper by means of a coated glass reflector (Oscillotracer†). When the tidal volumes were varied by adjustment of the cycling pressure of the respirator so that the end-expiratory volume remained the same and the end-inspiratory volumes were progressively increased, the points plotted on the pressure-volume co-ordinate system described lines, whose slopes represented the compliance of the structure (lungs or lungs and thorax) being studied. Figure 1 shows typical plots obtained on patient F.R. and normal subject J. W. for comparison. On the left the com-

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TABLE 1. *Respiratory Compliance in Poliomyelitic Patients with Respiratory-Muscle Paralysis.*

NAME	SEX	AGE	HEIGHT	WEIGHT	DURATION OF ILLNESS	VITAL CAPACITY	COMPLIANCE		
							LUNGS AND THORAX	LUNGS	THORAX
		yr.	*cm.*	*kg.*	*yr.*	*cc.*	*liters/cm. of water*	*liters/cm. of water*	*liters/cm. of water*
Patients:									
D. M.	M	16	180.0	46.0	¼	1400	0.070	0.080	0.120
P. B.	F	32	165.0	35.0	1¼	310	0.010	0.070	0.120
J. P.	F	22	166.0	37.0	1⅛	280	0.055	0.105	0.170
C. H.	F	17	171.5	48.0	1⅛	380	0.025	0.042	0.062
N. N.	F	37	170.0	42.0	¼	660	0.038	0.058	0.046
D. G.	M	21	178.0	50.0	1¼	800	0.070	0.100	0.100
F. R.	M	25	177.5	45.5	1⅛	240	0.070	0.057	0.196
Range ...		—	—	—	—	—	(0.025-0.065)	(0.042-0.105)	(0.062-0.196)
Mean ...		26	—	—	23/24	580	0.044	0.0717	0.122
Normal subjects:									
G. S.	M	28	179.0	79.0	—	5200	0.1	0.21	0.235
J. W.	M	38	188.0	86.3	—	6500	0.095	0.31	0.137
10 normal subjects[6]:									
Range					—	—	(0.05-0.17)	—	—
Mean					—	—	0.114	—	—
8 normal subjects[3]:									
Range					—	—	—	(0.16-0.31)	—
Mean					—	—	—	0.228	0.238*

*Based on compliance of lungs = 0.228 and on compliance of lungs and thorax = 0.114.

pliance plot of the lungs is represented and on the right that of the lungs and thorax.

Calibration of the pressure transducer was done before and after each patient study by means of water manometers. The pneumotachograph screens were calibrated directly at the beginning of the study so that known pressures were related to known rates of air flow. Later calibrations were done indirectly by application to the transducer of various pressures equivalent to known rates of air flow. The integrator was calibrated at a specific pressure or a specific signal sent into it, either of which was interrupted each second. By this means a pressure or a signal equivalent to a flow of 60 liters per minute gave a deflection on the oscilloscope screen equal to 1 liter of volume. If greater volumes were required, a signal of 300 liters per minute was used and a deflection equal to 5 liters was obtained.

Results

The results of the study, along with significant vital statistics, are presented in Table 1. The compliance values represent the slopes of the linear portions of pressure-volume plots similar to those shown in Figure 1, expressed in liters per centimeter of water. For a given subject the compliance of the structures studied is essentially constant over the range of tidal volumes encountered in normal ventilation. The range and mean compliance values for the lungs and thorax of 10 normal subjects, in addition to the 2 normal persons studied, are included. These have been obtained from the data of Rahn et al.,[6] who utilized a comparable method. The range and mean for lung compliance in 8 normal subjects obtained in this laboratory are included.[3] These values were obtained in the sitting position.

The compliance of all the respiratory structures in these poliomyelitic patients was markedly reduced. The lungs were on the average about a third as compliant as normal and the thorax about half as compliant as normal. The over-all compliance — that is, lungs and thorax — was about two fifths the normal value.

Discussion

Much of the emphasis in the therapy of chronic respirator patients has been directed toward the intercostal muscles, the diaphragm and the extensive articulations and joints in the thorax, since, as in the extremities, the joint capsules, tendons and muscles are the structures that are altered by the paralysis. Physiotherapy, accordingly, is aimed at correcting the changes that may have occurred, preventing deformity and maintaining freedom of motion. The same approach has guided physiotherapy of the thorax. The finding that the thoraxes in these patients are less compliant than normal subjects suggests that even more intensive therapy should be used to "loosen up" the thoracic structures and to maintain mobility.

The greatest change was observed in the lungs themselves, which showed an even smaller degree of compliance. The cause of this decrease of distensibility is not apparent, but several conditions might produce it. During the acute and subacute stages of the disease, atelectasis may occur, and the persistence of atelectatic areas would contribute to a decrease in compliance. Small areas of atelectasis with compensatory emphysema have been reported at autopsy in acute cases.[7-10] Such areas were not demonstrated on anteroposterior x-ray films of the chest in this group of patients.

The effects of body position should also be considered. Patients in a respirator are given only minimal degrees of motion and are virtually never turned onto their abdomens, a change in posture that would help to shift blood from the dependent portions of the lungs. The prone position is also best for tracheal drainage and might thus assist in the removal of mucus and the prevention of plugging of bronchioles, with resultant atelectasis. If position changes are limited or impossible, the use of an intermittent deep breath, as has been suggested,[11] might help to prevent atelectasis. It does seem unlikely, however, that such a maneuver would cause much shift of blood from the dependent portions of the lung. The accumulation of blood in these areas may lead to the formation of boggy tissue and atelectasis, which could produce the decreased compliance.

Respiratory movements produced by a respirator at the pressures usually employed operate within relatively narrow limits of the total lung capacity of a patient. Since the elastic properties of a system are in part determined by the stresses to which that system is subjected, it appears possible that the elastic properties of the lungs change because of their limited range of activity. These changes might consist of shortening and stiffening of the elastic fibers. A normal person takes frequent deep breaths or sighs in the course of a day and thus stretches the respiratory structures. This hypothesis offers an additional reason for an occasional deep breath in these patients.

These findings indicate that more intensive therapy should be directed toward the lungs, particularly in the stage of acute illness. Since all these patients showed the same abnormality, it appears that the changes occurred within the first three months after onset. In this small group there did not seem to be a striking relation between the duration of the illness and the loss of compliance. Some of the more chronic patients had lungs as compliant as those more recently afflicted. The reverse was also found to be true.

The question has been considered whether the chest compliance results could have been altered by voluntary action on the part of the patient. In

general, voluntary muscular action produces variable and grossly abnormal loops on the oscilloscope face; such patterns were easily detected and discarded.

A decrease of compliance increases the work of breathing. With the same effort a normal person achieves about two and a half times as much ventilation as patients convalescing from poliomyelitis. Since the patients have much less respiratory muscular power than normal persons, they are placed at an even greater disadvantage by the decreased compliance of their respiratory structures. Thus, any therapy that would increase the compliance of the lungs and chest would decrease the demands made upon the impaired respiratory muscles and facilitate more adequate ventilation of the lungs.

Summary

The compliance of the lungs and thoraxes (rib cage and diaphragm) in 7 chronic respirator patients has been shown to be considerably less than normal. The lungs were approximately a third as compliant as normal and the thoraxes approximately half as compliant as normal. Possible causes and methods of prevention of these changes are discussed. The implications of altered compliance of the lungs are discussed in terms of increased respiratory effort required of greatly impaired respiratory muscles.

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ADIPOSIS DOLOROSA (DERCUM'S DISEASE)*

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PHILADELPHIA

In 1892, Dercum[1] described 3 patients from the wards of Blockley Hospital with a peculiar malady, which he entitled "adiposis dolorosa," a syndrome to which his name has subsequently been affixed. Although many cases of adiposis dolorosa have been described in the literature,[2, 3-5] little has been added in clinical description, pathophysiologic interpretation or etiologic definition since Dercum's original publication. It is our purpose to report, from the birthplace of this disease, another case of adiposis dolorosa in which special studies were performed.

Adiposis dolorosa commonly affects menopausal women between the ages of thirty-five and fifty years. They are usually markedly obese at the time of onset, though weight loss and asthenia appear as the disease progresses, and severe emotional involvement is common. The disease is ushered in by noninflammatory, painful, subcutaneous tumors, which may appear at any site, except the face and head. Dercum[1] aptly described them as feeling like "a caked breast" or "a bag of worms."

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Case Report

M. B., a 37-year-old widow and the mother of 3 children, was admitted to the medical service of the Philadelphia General Hospital on March 13, 1950, with the chief complaints of pain in the legs and shortness of breath. She had been studied at another hospital in May, 1948, because of migratory polyarthritis, which was diagnosed as acute rheumatic fever. No previous episodes of this nature were recalled by the patient. In August, 1949, she was admitted to still another hospital because of palpitation and shortness of breath. The diagnoses of rheumatic heart disease, auricular fibrillation and congestive heart failure were made.

In November, 1948, the patient first noted a few hard masses in the anterior abdominal wall that became painful 1 month later. A biopsy of one of these nodules, on January 19, 1949 (performed at another hospital), was reported to reveal "proliferation of fibroblasts and round-cell infiltration in fatty tissue, showing some evidence of necrosis." Similar growths gradually appeared in the thighs and buttocks, and a concomitant loss of weight from 225 pounds to 130 pounds occurred.

There had been amenorrhea since July, 1949 (8 months), before which she had had 2 periods each month. Since September, 1949, shedding of head hair, marked fatigue and weakness had developed. In the 6 weeks prior to this hospital admission, night sweats, hot flashes and profuse perspiration were noted.

The patient, who appeared older than her stated age, was obviously seriously ill, but did not appear to be in acute distress. Dyspnea and orthopnea were present, but cyanosis was absent. The blood pressure was 112/86; the temperature was 98.4°F.; the respiratory rate was 28. Severe congestive heart failure was evident, with distended neck veins,

enlarged and tender liver, +++ pitting edema of the ankles, moist rales at both lung bases and an enlarged heart, the border of cardiac dullness extending to the left of the anterior axillary line. The rhythm was irregular, with an apical rate of 148 per minute and a radial rate of 120 per minute. A systolic murmur and a diastolic gallop were heard at the apex.

FIGURE 1. *Appearance of Patient.*
Note the lumpiness of the thighs and buttocks, representing subcutaneous collections of painful fatty tissue. The darkened areas are the result of cutaneous ecchymoses.

Pubic and axillary hair was sparse. The breasts and pelvis were normal except for mild atrophy of the labia and corpus uteri. Neurologic and ophthalmologic examinations were negative.

In the subcutaneous tissue of the anterior and medial aspects of the thighs, of the anterior abdominal wall and of the buttocks, multiple, firm, tender, freely movable masses were present. Some felt like the typical "caked breast"; others like the "bag of worms." The skin overlying the exquisitely tender masses in the thighs was ecchymotic. The patient's appearance is shown in Figure 1.

An electrocardiogram confirmed the presence of auricular fibrillation. X-ray study of the chest showed an enlarged heart with a straight left border and hilar and basilar congestion. The barium-filled esophagus was markedly displaced by the left auricle in the oblique view. Examination of the blood revealed a hemoglobin of 12.1 gm. per 100 cc. and a white-cell count of 8350, with 80 per cent neutrophils and 14 per cent lymphocytes. Repeated blood counts during hospitalization were within normal limits. Bleeding and clotting time, blood culture, agglutinations for typhoid and paratyphoid fever, salmonella and brucella, heterophil-antibody, cold agglutinins and upper and lower gastrointestinal x-ray series were all within the normal range. The results of endocrine studies are presented in Table 1.

The congestive heart failure responded rapidly to diuretics, digitalis and a low-salt diet. Pain was partially relieved by tetraethylammonium chloride (200 to 300 mg. intramuscularly), aspirin and phenobarbital, but codeine was finally required. Points of maximum pain and tenderness were inconstant, shifting variously from the thighs to the buttocks. One large mass in the left buttock became necrotic, and sloughing resulted.

The patient was at all times unhappy, tearful and complaining.

On May 27, 1950, a biopsy, taken from one of the painful lumps in the left thigh, revealed well differentiated fat tissue showing some infiltration of plasma cells and perivascular precipitation of calcium. This was considered compatible with adiposis dolorosa. The wound healed uneventfully.

A 4-day course of adrenocorticotrophic hormone, 80 mg. the 1st day and 60 mg. a day thereafter, caused no subjective or objective improvement.

Because of the favorable reports in the literature[3] concerning the efficacy of thyroid medication, 0.06 gm. (1 gr.) of desiccated thyroid daily was begun on June 21. The patient showed no increase in pulse rate, but on June 26 she became dyspneic and moist rales developed in the chest. The temperature rose rapidly to 105°F., and the patient died. Permission for post-mortem examination was denied.

DISCUSSION

In 1892 Dercum[1] wrote, "Not only is the development of the enlargement irregular and even capricious in these cases, but there is, in addition, another important factor to be remembered, and that is: that at some time or other, the enlargement is accompanied by pain or other nervous symptom." Later writers[3-5] have confirmed the concept that irregular, painful, subcutaneous deposits of fat constitute the primary symptom complex of this disease.

TABLE 1. *Results of Endocrine Tests in a Patient with Adiposis Dolorosa Compared with Normal Values.*

	I^{131} Tracer[12] Uptake	Serum Cholesterol	Cholesterol Esters	Serum Calcium	Inorganic Phosphorus	Alkaline Phosphatase	Serum Sodium	Serum Potassium	Serum Chloride	11-Oxysteroids[13]	17-Ketosteroids[14]
	%/24 hr.	*mg./100 cc.*	*% total cholesterol*	*mg./100 cc.*	*units/100 cc.*	*units/100 cc.*	*milliequiv./liter*	*milliequiv./liter*	*milliequiv./liter*	*mg./24 hr.*	*mg./24 hr.*
Patient's values	29	122, 120	89 (74)	9.7	3.53	3.09	134	4.9	97	1.1, 0.3, 0.3	1.6, 3.5, 3.6
Normal values	10–35	110–300	60–80	9.0–11.5	3.0–4.5	1.5–4.0	128–151	4.3–5.3	97–106	0.9–2.0	5–15*

*In female patients.
†Epinephrine administered subcutaneously.
‡In menopausal patients.

Other features are more variable, including findings attributed by earlier writers to myxedema — for example, lack of sweating, coarse, dry skin and loss of hair. Epistaxis, weakness and irritability have frequently been described. The signs and symptoms of congestive heart failure are quite common. These have been considered to be due to fatty infiltration of the heart, though the evidence for this appears tenuous. Dercum[1] relates that 2 of his patients had cardiac dyspnea. The pulse rate in 1 varied from 95 to 110 per minute. He describes the pulse of the other as "irregular and intermittent"; cardiac enlargement was found at autopsy in this case, and thickening of the mitral and aortic values was present in another. The heart substance was described as being "evidently fatty." Microscopical examination was not performed.

Of the 2 cases reported by Price[4] in 1909, 1 had a history of rheumatism in the wrists and knees on several occasions and an aortic systolic murmur that was transmitted to the neck. The other patient had frequent attacks of dyspnea and cyanosis and a hypertrophied heart at post-mortem examination.

In 1938 Wohl and Pastor[6] reported 3 cases of adiposis dolorosa in which marked generalized weakness was the major complaint. In 2, a myasthenia-gravis type of response to faradic stimulation of striated muscle was found. These authors believed that all 3 cases responded to therapy with prostigmine and aminoacetic acid. Myographic studies were not performed in the case reported above, but on purely clinical grounds there was no evidence of myasthenia gravis.

It is surprising that biopsy of the clinically obvious tumefactions does not reveal more specific histologic abnormalities. This is in accord with studies using special fat and nerve stains[7] in which no abnormality was found in biopsies in 6 cases of adiposis dolorosa. Chemical analysis of the fat has also proved unrevealing.[8]

Although earlier writers[4, 5] considered the disease to be a form of myxedema, more recent studies make it appear unlikely that hypothyroidism plays any important etiologic role. It appears that those who have claimed efficacious results from various therapeutic agents have neglected the one factor that is common to patients who have survived and improved, — namely, weight reduction.[5] Moreover, many of those reported to have recovered have had painful obesity but have not had the typical nodular fatty deposits described by Dercum.

By 1925 the concept was generally held that the origin of adiposis dolorosa was a pluriglandular disorder, because of the reports of thyroid, pituitary, pancreatic, adrenal and ovarian abnormalities found at post-mortem examination.[9] In the light of present knowledge, the significance of many of these findings is doubtful. Wilson,[10] in 1933, could discern no consistent pattern in the pathological findings reported and thus considered the glandular changes to be coincidental rather than etiologic. Nevertheless, most of the victims of this disease are prematurely amenorrheic. The patients in 2 of Dercum's cases stopped menstruating at thirty-five years of age. The patient in the case reported above was thirty-six years old when menstruation abruptly ceased. The sparsity of pubic and axillary hair and the increased loss of hair from the scalp also raised the question of an endocrine disorder. For these reasons, an endocrine survey was performed with the co-operation of Dr. William H. Perloff, chief of endocrinology of the Philadelphia General Hospital (Table 1). We believe that this is the first case of adiposis dolorosa to be studied with modern endocrine technics.

Thyroid function, as evidenced by the uptake of I^{131} and the serum cholesterol, was normal; serum calcium and phosphorus values indicated unimpaired function of the parathyroid glands. The consistently low urinary 17-ketosteroids and 11-oxysteroids and the slightly increased insulin sensitivity suggest some hypofunction of the adrenal glands. The one normal 11-oxysteroid value, which was obtained shortly after admission and after mer-

TABLE 1. (*Concluded.*)

	Insulin Tolerance[15]						Glucose Tolerance					Fall of Eosinophils		Estrogens[17]	Gonadotrophins[16, 12]
	Fasting	30 min.	45 min.	60 min.	90 min.	120 min.	Fasting	30 min.	60 min.	2 hr.	3 hr.	4 hr. after insulin	4 hr. after epinephrine[16]		
	Blood Sugar in														
	mg./100 cc.	*mg./100 cc.*	*mg./100 cc.*	*mg./100 cc.*	*mg./100 cc.*	*mg./100 cc.*	*mg./100 cc.*	*mg./100 cc.*	*mg./100 cc.*	*mg./100 cc.*	*mg./100 cc.*	%	%	*mouse units/24 hr.*	*mouse units/24 hr.*
Patient's values	100	66	57	73	75	75	66	105	118	129	100	63	65	13, 13	0, trace, 0
Normal values	Not more than 50% decrease in 30 min., returning to fasting level in 2 hr.						Rise to not more than 160 mg. per 100 cc., returning to fasting level in 2 hr.					>50	>50	2–13‡	125‡

curial therapy with resulting diuresis, may be explained by the fact that increased corticoid excretion after mercurial diuresis has been observed in patients with fluid retention.[11] However, the eosinophil response to insulin and epinephrine suggests a normal adrenal response to stress, and leads to the conclusion that the decreased excretion of adrenocortical hormones was not on the basis of a primary adrenal deficiency, but rather secondary to the general debilitation and malnutrition exhibited by the patient. This is also the likeliest explanation for the slight prolongation of the elevated blood sugar level in the glucose tolerance test. The A value, measuring the ability of the adrenal gland to respond to a water load, was normal.

The low urinary estrogen values were consistent with the patient's amenorrhea and symptoms suggestive of the menopause; however, the fact that gonadotrophin values typical of the climacteric were not found in this case suggests that the ovarian failure was secondary to pituitary underfunction, which in turn resulted from the cachexia.

In conclusion, although the endocrine survey of this patient revealed some degree of hypofunction of the adrenal cortex, pituitary and ovaries, it presented no good evidence that the etiology of adiposis dolorosa is endocrine in origin inasmuch as the endocrine changes similar to those noted have been observed in cases of chronic illness of varied etiology.

Summary

A case of adiposis dolorosa (Dercum's disease) is presented. This condition is characterized by the presence of painful, nodular accumulations of subcutaneous fat in amenorrheic, neurotic women.

The frequent association with rheumatic heart disease is noted.

An endocrine survey gave no conclusive evidence that the disease results from a primary disturbance of endocrine function.

A short course of ACTH therapy did not result in improvement.

The etiology of adiposis dolorosa remains undetermined.

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STATE COLLEGE OF AGRICU... SEP 22 ... MANHATTAN KANSAS SCIENCE

MEDICAL PROGRESS

DIABETES MELLITUS (Concluded)

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BOSTON

TREATMENT OF DIABETES

Since the introduction of insulin, both acidosis and symptoms can now be easily avoided. There is, however, incomplete agreement about the aims of therapy — namely, whether or not to achieve normoglycemia. The results of those advocating a completely free diet with insulin have hitherto never been published in sufficient detail. Forsyth et al.[78] surveyed the use of such a regime for five years in 47 insulin-treated cases, and, even with a *laissez faire* attitude, 11 had to be returned to dietary control because of weight gain, rising blood sugar and insulin requirements and frequent reactions. Detailed analysis of the eating habits of those on free diets revealed the surprising fact that they maintained a fairly constant diet most of the time, the crucial deviations being of a sporadic character, mostly on week ends.

To ascertain the relative frequency of the various degrees of control actually in use today, Beaser[79] polled a third of the members of the American Diabetes Association. This revealed that 70 per cent aimed for aglycosuria or better. They found that they could accomplish this ambitious goal with relatively simple diet technics, using household servings and exchange lists and not requiring weighing of food. Yet, paradoxically, the remaining physicians who were satisfied with glycosuric control still used essentially the same methods to achieve this; very few used free diets.

As for the diet itself, the present long-acting insulin makes protein and fat important largely for their caloric content. In the patient with stable diabetes, the total carbohydrate content is still somewhat reduced, but its distribution among the meals is relatively normal and its quantity from day to day need only be reasonably constant,† not absolutely accurate in amount. It was the logical next step to apply a parallel simplification to the calculation methods used by physicians for prescribing diets.[80, 81]

NPH insulin, introduced in the past two years, has the action of one part of regular and two parts of protamine zinc insulin. Although it took a decade for the latter to reach its maximum use, acceptance of NPH has been at a more rapid pace.‡ This is due to its applicability to diabetes of all degrees of severity.

In severe but stable diabetes, NPH can be substituted with increased efficiency for globin or protamine zinc insulin[82] or mixtures of the latter with regular insulin.[83] Even in some of the severe but unstable cases, Izzo and his associates[82] found NPH to equal the efficiency of 2:1 mixtures. In diabetic patients hospitalized with nondiabetic complications that make the diabetes unstable, the early use of NPH is recommended to decrease the fluctuations of the blood sugar and accelerate final regulation.[84]

Whereas NPH was found adequate for the treatment of the above groups, which comprise approximately 75 per cent of all insulin-treated diabetic patients, it proved to be inadequate for the remaining 25 per cent whose disease was too severe and unstable. Dolger[85] studied a group of 186 patients with severe diabetes,§ of whom 72, or almost 40 per cent, fell in the latter category. He made up extemporaneous mixtures for them in various ratios of protamine zinc insulin and regular insulin and found that a majority required more protamine zinc insulin action than was contained in the NPH and a minority more regular action. To obtain longer action, one must revert to calculated mixtures of protamine zinc and regular insulin; to obtain more regular action, the regular insulin can be added directly to the NPH, and all its intense effects still remain intact.

Theoretically, all diet-treated and over 80 per cent of insulin-treated diabetic persons could achieve normoglycemia; in actual practice only a minority do so. The main difficulty is the inability of the patient to restrain his appetite urge to a reasonable dietary constancy as defined above. A report on the use of anorexigenic drugs (d-amphetamine sulfate) in diabetes indicates a certain degree of success, with a relapse rate of two thirds one year after cessation of therapy.[86]

The basic difficulty is psychologic rather than physiologic. The relation of emotional stress to diabetic physiology has been studied in detail in both severe, juvenile, and mild, adult, diabetes.[87-90] Such stress can upset regulation indirectly by the mechanism of overeating. However, especially in youth, it may do so by direct, immediate metabolic effects such as ketonemia, hyperglycemia and diuresis, singly or in combination. These laboratory

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†Reasonable constancy is about ± 15 per cent, equaling the variability of the household-serving technic of food measurement and that of the carbohydrate content of the common foods.

‡Personal communication from Dr. F. B. Peck, of Lilly Research Laboratories: previously relative sales were 1/3 regular and 2/3 protamine zinc insulin; today ¼ NPH, ¼ regular and only ½ protamine zinc insulin.

§These patients used a total of 40 to 160 units of insulin daily, and 30 per cent were under eighteen years of age.

studies confirm previous clinical impressions regarding such relations. For some time at the Beth Israel Hospital, the psychiatric staff has participated in the diabetic outpatient department on an informal basis. Even superficial examination by the medical staff has revealed that a variety of psychiatric and environmental factors are important in influencing the diabetes through food intake. Only infrequently, particularly in juvenile cases, has it been necessary to refer the patients for specialized psychiatric therapy.

It is important to bring up to date reports on the status of recently advocated therapeutic adjuncts in diabetic therapy. The jet-injector technic is not yet perfected to the point of practical use.[91] The initial claims for the therapeutic usefulness of insulin pellets,[92] choline,[93] inositol[94] and vitamin E[95] have not been substantiated.

Diabetes and Associated Diseases

Miscellaneous Conditions

It is of interest that 3 cases of so rare a disease as acute porphyria have been reported in diabetic patients; confusion is possible because of the presence of neuritis in both.[96] However, the alleged increased incidence of diabetes in Paget's disease has not been confirmed.[97]

Tuberculosis is still a frequent (11 per cent) cause of death in young diabetic persons.[98] The recent Philadelphia survey shows that the incidence of all cases of tuberculosis is twice as great and of the active disease three times as great among living diabetic patients as among nondiabetic persons.[99] This report confirms again the fact that it attacks the young (under forty years of age) and those with undernutrition. This indicates the need for frequent chest x-ray examinations and good nutrition in this susceptible group.

Surgery in Diabetes

The diabetic patient undergoing surgical trauma is less well prepared than the normal person so far as nutritional reserves and the electrolyte balance are concerned. For such patients, therefore, it is doubly necessary to strive for these objectives. The avoidance of significant ketonemia is not a vital objective by itself but serves as a convenient index of optimum metabolism. Wren and Sachar[100] have shown that 200 gm. of glucose per day is optimum for the accomplishment of this end by parenteral therapy in the nondiabetic person. On the other hand, others have shown that as much as 25 to 50 per cent of such parenterally administered glucose may be lost in the urine of nondiabetic patients,[101,102] and the accompanying diuresis may contribute to cellular dehydration and potassium losses. Since the utilization of fructose is considerably better than glucose, it has been recommended that it be substituted in *all* postoperative cases in the form of a 10 per cent solution of fructose[103] or a 5, 10 or 15 per cent solution of invert sugar.[102, 104] This would be doubly pertinent in diabetic patients, in whom the margin of superiority of fructose over glucose utilization is even greater.

The pathogenesis of the potassium-deficiency syndrome in the nondiabetic surgical patient may be related to several factors: acute hyperactivity of the adrenal cortex, cellular dehydration, sodium-potassium interchange in damaged muscles[105] and losses of potassium-containing intestinal fluids. In diabetes, the low adrenocortical function may minimize the first, but the second and the third are at least equal and even excessive. The tendency to acidosis and gluconeogenesis from protein exaggerates these even further. Accordingly, the parenteral administration of potassium-containing fluids in diabetic patients undergoing operation is even more definitely indicated than in nondiabetic persons; such fluids have been recommended for the latter not only after potassium deficiency has been recognized but also as a prophylactic routine.[106, 107]

Pregnancy in Diabetes

The increased incidence of fetal and neonatal* mortality continues to be the main problem in pregnancy among diabetic mothers. White's[108] series of 439 cases of pregnancy in diabetes that resulted in living infants, reported in 1949, emphasized long duration of the diabetes and hormonal imbalance as important unfavorable factors. She claimed that therapy of the latter was principally responsible for a reduction of the perinatal loss to an all-time low of 11 per cent.[108] However, no controls were presented, and the role of improved obstetric management was not considered.

Since then, several large series of pregnancies among diabetic patients have been reported without the use of hormone therapy. Two of them succeeded in reducing the perinatal mortality rate to 18.3 per cent and 13.6 per cent by careful management alone; the authors estimated that further improvement of this factor alone could be expected to reduce future mortality figures to 7.6 and 10 per cent respectively.[109, 110] A very recent report by Miller[111] also showed the low mortality of 14.8 per cent, and that of a carefully managed subgroup was only 10 per cent. This was also the rate among patients delivered by cesarean section, who constituted 60 per cent of his series. Yet Miller opposes the routine use of this procedure. Instead, his analysis located the greatest mortality among the oversized and undersized babies and concluded that the mortality could be reduced to 9 per cent by careful individual management of these cases. This still left an as yet uncorrectable residue due to congenital defects and other unidentified causes. Both he and Reis et al.[110] showed the effect of such specialized obstetric management in a 66 per cent and 50 per cent reduction respectively in the perinatal deaths among the patients of their own series as compared

*These are hereafter combined under the term perinatal.

with previous pregnancies of the same patients elsewhere.

Miller pointed out that there remains little significant difference between White's series and the others to attribute to the benefits of parenteral hormone therapy or to justify its routine use. In fact, recent work has shown that estrogenic therapy results in an increase in the size of the fetus[112] and placenta[113] that would be undesirable in diabetes. The average duration of the diabetes was longer in White's series than in that of the others, and this may have added significance to her better results. However, doubt has recently been expressed about whether this factor really has a significant effect on the mortality rate.[111, 114, 115]

These latest series have also shown the advantage of the avoidance of acidosis. This factor is given full responsibility for any increased incidence of early abortion in diabetes[109]; it was the cause of 35 per cent of the perinatal deaths among the infants of insulin-treated mothers in a series treated by the free diet method.[116]

Complications

Metabolic Acidosis

A number of recent studies have contributed to a better understanding of the physiologic mechanisms of diabetic acidosis. For example, Fisher[117] produced elevated blood acetoacetic acid levels in rabbits equal to that in human coma, and yet toxicity was not significant. In human diabetic acidosis, he did find a rough correlation between the mental state and blood ketone levels,* so that the latter may serve as a convenient index of the cerebral metabolic abnormalities even though it does not reveal the direct cause. The basal metabolic rate has been shown to be definitely increased in coma, more as a reflection of the deranged and inefficient oxidative mechanisms than as a result of simple hyperpnea.[119] It has been shown that experimental potassium deficiency (in rats)[120] or simple acidosis[121] can strikingly decrease the efficiency of carbohydrate metabolism. Thus, once initiated the uncontrolled diabetic state has the potentialities of a vicious circle.

The shock-like state of diabetic coma with an irreversible decrease in blood pressure has previously been shown to be peripheral rather than central in origin.[122] A similar condition has been reproduced by an induced state of acute acidosis (by acid sodium phosphate) with a resultant reduction in peripheral resistance, increased cardiac output and hypotension.[123] No significant shifts in other electrolytes were noted in these experiments. Thus, the simple determination of blood pH could serve better than more complicated tests to mirror the gravity of both the cardiovascular and the cerebral status of the patient in diabetic coma.

*Kety[118] had previously found the best correlation with cerebral oxygen consumption, blood ketone level and pH in that order.

Potassium deficiency of sufficient degree is known to decrease cardiac function directly. Recently, digitalis toxicity was shown to be potentiated in man by an acute loss of potassium through mercurial diuresis.[124] Since blood potassium levels were unchanged and since the effect could also be produced by insulin and glucose administration without diuresis, it was believed that the mechanism was one of a change in tissue, not one of serum potassium levels.

The therapy of diabetic acidosis is becoming less controversial as it becomes more firmly based on sounder physiologic observations. The role of glucose in such therapy is an example. At *moderate* rates of administration glucose can be utilized in coma, and such amounts do not necessarily cause significant potassium diuresis.[125] However, from a practical point of view, the value of large amounts of glucose intravenously to "increase glucose utilization" has been disproved; in fact, because of its strictly extracellular role,[10] this may prove harmful by increasing cellular dehydration. The problem of glucose administration in acidosis can be summarized as follows: only in a small proportion of cases of coma, with a relatively low blood sugar level (below 300 mg. per 100 cc.) would glucose be useful at the initial stage of therapy; and then, if given in small amounts, it would be harmless. For the rest, it is best to begin therapy with hypotonic solutions without glucose[126]: this procedure would at the same time correct the important dehydration and preserve the blood sugar as a useful index of the progress of therapy.

The estimate of potassium deficit in diabetic acidosis has been revised upward to an average of 10 gm. or more to be replaced in the first twenty-four hours. Such deficiency can be diagnosed before symptoms by the use of blood estimation or by the electrocardiographic changes.[127, 128] The usual time of occurrence is from the third hour of therapy onward. The more advanced method of coping with this problem is to replace potassium prophylactically at a slow rate and in low concentrations in the routine solutions used intravenously after the fourth hour of therapy or after kidney function is assured, whichever is latest.[129-131] Using the solutions as advocated by Butler, Harwood[132] has effected a very satisfactory decrease in the mortality from coma at the Massachusetts General Hospital — from 20 to 1.5 per cent.

The decreased effectiveness of insulin in diabetic acidosis may be a formidable factor in prognosis. This may be related to increased adrenocortical activity (as measured by urinary corticosteroid excretion), which occurs in the later stages of coma, but not in the early phase.[133] This takes three to five days to return to normal after the acidosis has been dissipated. However, this mechanism is not at the root of the usual variety of insulin resistance.

Degenerative Conditions

The relative importance of the diabetic complications has increased. In the past two decades the incidence of deaths from cardiovascular disease has increased from 32 to 50 per cent among adult patients with diabetes[134] and from 8 to 38 per cent among juvenile diabetic patients.[98] Among the latter, nephropathy has increased from 12 to 37 per cent.

Many surveys have been undertaken to determine the important factors in the pathogenesis of these complications. Studies of characteristic complications such as retinitis, nephropathy and cataracts in youthful diabetic patients could lead to more conclusive results than a similar study of the arteriosclerotic complications in the aged. One such conclusion has been that the longer the duration of the diabetes, the greater the incidence of retinitis and nephropathy after ten and especially after twenty years of diabetes.[135, 136]

Given the same set of facts regarding the origin of diabetic complications in human diabetes, two sets of interpretations are usually offered. One is that the complications as well as the diabetes stem from a common source so that the former are inevitable and not preventable.[137] The other point of view holds that the complications arise from the diabetes and are particularly related to the degree of deviation from excellent regulation. This point of view postulates that one (or more) of the myriad of metabolic aberrations occurring in poorly controlled diabetes is the probable biochemical factor responsible for a given complication and that hyperglycemia can be used as a rough measure of this factor.

It has recently been shown that purely pancreatic diabetes in animals eventuates in such complications as cataracts[138] and nephropathy,[139] and this argues against the first interpretation. Moreover, such experimental cataract formation can be shown to be related not merely to the duration of the diabetes but also to the degree of hyperglycemia.[138] In human diabetes, too, not only the duration but also the degree of control has been shown to be significant in the development of retinitis, nephropathy and hypertension.[135, 136, 140, 141] Cataract formation, by contrast, seems to follow relatively short periods of greater lack of control, such as acidosis and coma.[135] With good or excellent control complications may be absent even after twenty years or more of diabetes.

The complexities of the pathogenesis of atherosclerosis and arteriosclerosis are beyond the scope of this paper. However, certain facts pertinent to diabetes can be examined with profit, especially the evidence for specific abnormalities of lipid metabolism. Diabetic persons have abnormally increased blood concentrations of total blood lipids,[142] blood cholesterol[135] and large molecular lipoproteins,[143] especially when the disease is not carefully controlled. How well controlled the diabetes must be to neutralize each or all of these factors is not clear, but clinical observation indicates that individual predisposition is as important as general rules. The fat-tolerance test can be used as an index of the abnormality of lipid metabolism in diabetes.[144] A fatty meal is administered, and the rise in serum esterified fatty acids is measured. The curve of the diabetic person is seen to deviate from the normal in a manner generally similar to the results of the glucose tolerance test.

The increased incidence of coronary-artery and peripheral vascular disease among diabetic patients does not have its counterpart in the cholesterol content of the aorta itself.[145] The final proof of the relation of the *control* of diabetes to coronary arteriosclerosis is still lacking. A survey of 100 consecutive living adult diabetic patients in the Beth Israel Hospital clinic, still unpublished, showed significant degrees of ischemia or thrombosis of the cerebral, coronary or peripheral vascular tree in 50 per cent; the two circumstances that seemed independently to increase their incidence were sex (maleness) and poor control.

There have been certain clinical advances in the handling of the peripheral vascular complications. Surgically, lumbar sympathectomy, although helpful for intermittent claudication, has not shown decisive results in impending or actual gangrene.[146] Conservative amputations are more successful than hitherto because of the newer antibiotics; in fact, the combined use of antibiotics with enzyme therapy has facilitated the healing of local peripheral lesions that would previously have required at least local amputation.[147]

Renal Lesions

The increasing incidence of intercapillary glomerulosclerosis as the cause of death in all diabetic patients, especially the young, makes this complication of paramount importance. This term is a pathological one, and its use for the clinical syndrome* originally described by Kimmelstiel and Wilson is not ideal. For example it has recently been pointed out that the pathological findings in a series of such patients frequently include infection or arteriolosclerosis as well as the characteristic focal glomerular hyaline bodies.[148, 149] The proposed substitution of the term diabetic nephropathy would also be unsatisfactory in that it implies without exact proof the diabetic origin of the additional two degenerative findings. In experimental alloxan diabetes (in the rat), renal lesions are also found: the earliest are an intense increase in the reticulin fibers of the glomerular capillary walls and later obliteration of the capillaries and fusion into an amorphous

*This includes some features of nephrosis, uremia or hypertension, separately or in combination.

mass.[139, 150] The characteristic hyaline globules are not present in this species.

In the speculation regarding the pathogenesis of this condition, the close relation to retinitis has been considered significant. Clinically, 75 to 90 per cent of diabetic patients with nephropathy also have retinitis — double the incidence in diabetes generally.[151, 152] Pathologically, the advanced hyaline renal lesions are practically always accompanied by retinal aneurysms demonstrable by injection. This led Ashton[153] to inject such kidneys with India ink and to demonstrate what he regarded as aneurysms in the glomeruli in close association with the hyaline masses.

Pathologically, advanced renal lesions in diabetic patients are set apart from those in nondiabetic patients by a significant increase in stainable lipids. It is present in the glomeruli of intercapillary glomerulosclerosis in globular shapes and parallel in degree to the hyaline changes.[154] Also outstanding are the deposits in advanced arteriolonephrosclerosis in diabetes*; these appear as streaks along the arterioles and are not doubly refractive.[155] The combination of excess lipid in both those locations is almost characteristic for diabetes. Wilens and Elster[155] regard lipids as precursors of the hyalinization in each case.

A general correlation may be found between the clinical and pathological findings in diabetic nephropathy. The full clinical syndrome was not seen in the absence of the glomerular lesions, but 4 out of 5 cases with significant degrees of diabetic nephropathy had no clinical findings or only proteinuria,[149] which is the earliest finding and practically always precedes the hypertension.[98] Although mild or moderate lesions may be present without proteinuria, high degrees of proteinuria (+++ or ++++ reaction) almost invariably mean an advanced pathologic process. The accompanying diabetes is mild in half the adult cases.[149] From a study of the entire diabetic history of patients with this disorder, the diabetes, for no known reason, has been shown to become milder as the renal disease progresses.[156]

Search for pathogenetic factors in this complication may be more fruitful in the diabetes of the younger age group, which is normally less subject to degenerative disease. A positive correlation for the development of nephropathy was found for both duration and poor control of the diabetes.† [148] The figures were striking: in 49 per cent of those with poor control nephropathy developed, but it was not found in a single 1 of 37 patients with good control. It was also shown that, on the average, proteinuria is the earliest manifestation of this condition, appearing fourteen years after the onset of the diabetes. The average patient shows edema three years after the detection of proteinuria, congestive failure in four years and death in about five years.[148] In another series of 1335 diabetic patients of all ages, diabetic nephropathy developed in 10 per cent, almost all of whom died two to seven years after diagnosis.[157]

Renal-function tests in diabetes without albuminuria or other evidence of renal disease may show (in 3 out of 10 patients) glomerular filtration rates ranging from 55 to 70 per cent of normal.[158] In 9 patients with diabetic nephropathy an even more severe depression of the filtration rate was found in all, but an extensive battery of such renal-function tests did not help differentiate diabetic nephropathy from chronic glomerulonephritis.[159] Accordingly, hypertension, albuminuria and doubly refractive lipoid bodies in the urine are as helpful as more complex tests in differential diagnosis. Two new therapeutic measures have been introduced in non-diabetic nephrosis — namely, cation-exchange resins[160] and cortisone[161]; in diabetic nephropathy, the former has also proved helpful,[162] but the latter has not.[163]

Experimental papillary necrosis of the kidneys similar to that in diabetes has been produced in normal dogs by the procedure of obstructing one or both ureters while life is prolonged by means of a low-electrolyte diet and the artificial kidney.[164] The fundamental lesion is a pressure obstruction of the medullary vessels, with consequent ischemic necrosis of the papillae. Clinically, in nondiabetic subjects the process is first some degree of obstruction of the ureters and then secondary infection; in the diabetic patient, the infection is primary, and the resultant interstitial edema and inflammation block the same set of blood vessels. Basically, then, the disease is a severe variant of the familiar pyelonephritis to which diabetic persons are susceptible, and the therapy is based on a vigorous chemotherapeutic program, preferably prophylactic. In unilateral disease, surgery may give relief if the diagnosis is made early enough.

Retinitis

The pathology of diabetic retinitis has been further clarified by the technic of India-ink vascular injection — in some cases, the arteries with red and the veins with black ink. The microaneurysms were clearly outlined, and some were found in nondiabetic conditions, mainly thrombotic glaucoma and chronic uveitis.[153] In diabetes, they were located principally on the venous side, at the junction of the venules and arterioles. By use of this and other criteria such as extensiveness and retinal location, diabetic aneurysms could definitely be differentiated from the nondiabetic variety.[165]

In retinitis, too, poor control has been added to long duration as a significant predisposing factor. In a recent series of 150 cases of diabetes of fifteen to twenty-six years' duration almost half the pa-

*The only other condition showing this is the arteriolonephrosclerosis of essential hypertension.

†This was also true for the development of the not entirely similar kidney lesions in the diabetic rat.

tients had retinitis. Among these cases the condition had developed in 72 per cent with poor diabetic control as contrasted with only 28 per cent with good control.[166] As in other complications, the factor of individual predisposition is probably involved.

Therapeutically, well controlled studies have shown rutin to be ineffective,[167, 168] and the reason may well be the lack of absorption of this material as well as its ineffectiveness.[169]

Cataracts

A considerable improvement in the technic of growing the rabbit lens in vitro has facilitated the detailed study of its metabolism.[170] With C^{14} aminoacetic acid in the surrounding medium, it was shown that both protein and glutathione are continuously being synthesized from their constituent amino acids.[171] Glutathione has long been known to be strikingly decreased in human and experimental cataract. By the same method, the lowered glutathione content of the experimental (naphthaline) cataract was shown to be a result of an inhibition of its synthesis. Another approach to the problem has been a study of the enzyme systems in homogenates of normal lens and micro-wave-produced animal cataracts.[172] In the animals with such cataracts there was decreased hydrolysis of inorganic pyrophosphate and decreased dephosphorylation of adenosine triphosphate.

Diabetic cataract appears in alloxan-diabetic animals, and it also has a lowered glutathione content, which is unrelated to the immediate and temporary decrease in blood glutathione that follows alloxan injection.[173] This type of cataract appears in alloxan-diabetic rats only if the blood sugar is high enough (over 225 mg. per 100 cc.) and after a minimum duration (thirty-six days) of the diabetes.[174] There seems to be a consistent pattern in the appearance of these two pathogenetically important factors in diabetic nephropathy, retinitis and cataracts. In diabetic rats, the younger the age, the greater the tendency to cataract formation.[138, 175]

Diabetic Neuritis

Recently, progress has been made in the understanding of this complication. By the use of a quantitative measurement of vibratory sensation, it has been shown that normally this index decreases with age, but the decrease at any age is greater in diabetic persons.[176] At the onset of therapy in a new case of diabetes, vibratory sensation shows a measurable decrease within the first month of therapy.[177]

Both vitamin B_{12} in adequate dosage[178, 179] and a new liver extract* [180, 181] have had a striking success in the treatment of diabetic neuritis. Both are effective within a few days and have been found useful even in cases of long standing, usually considered to be "vascular" in origin and therefore irreversible. The dose of vitamin B_{12} used (15 to 30 microgm. daily) was greater than that used previously, and this may account for the present success. Relapses may occur with both. BAL has likewise been found efficacious recently.[182] The very diversity of the therapeutic agents may be helpful in revealing their common point of action in this disabling disorder.

*A water-soluble extract of mammalian liver called "Hepulin," which is practically devoid of vitamin B_{12}.

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MEDICAL INTELLIGENCE

REVOLUTION IN FICTION

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A phenomenon that none foresaw and few seem to be able to understand confronts the literary critics. A young, Brooklyn-born veteran of World War II with little previous experience as a writer and no regard for tradition has almost swept the crime-novel field clean. He is Mickey Spillane, author of half a dozen yarns centering on the doings of Mike Hammer, a private eye.

Spillane, and his predecessors, Dashiell Hammett and Raymond Chandler, are unfavorably scrutinized in a recent article entitled "The Decline and Fall of the Whodunit" by Ben Roy Redman.* Hammett and Chandler are said to have begun the decline, but the fall is placed on Spillane's shoulders. This is an interesting point of view that will not necessarily be shared by all physicians, some of whom may be devotees of this bloody trio of writers. The reading public, in general, probably does not share it since, in less than four years, the sale of Spillane's books is advertised to have reached the astonishing total of 11,000,000 and, it is claimed, has netted the author upward of $300,000. This is enough to make anyone cast about for a likely explanation.

The literary merit of the volumes is clearly not the reason. Hardly a critic has failed to attack Spillane for his style and grammar. Nevertheless, Spillane has avoided the fatal error of developing his style to the detriment of the narrative. He is a master storyteller; yet one has to look elsewhere for the key to his success. The search need not be prolonged. It is clear that the Spillane secret is the tabloid secret: he supplies minute descriptions of murders, savage beatings and uninhibited sexual exploits in great abundance. His hero is a sadist operating behind a semi-legal façade, a self-appointed sleuth, judge, jury and executioner. It is not the chase that delights the hero; it is the execution. When he is killing, or on the point of doing so, the thoughts that run through Hammer's mind resemble what a psychoanalyst probably would have heard had he analyzed Jack the Ripper. Hammer's pleasure becomes exquisite if he finds it necessary to slay or brutally beat several other persons, male or female, in his search for the guilty one. On his way, he invariably consumes prodigious quantities of liquor and is seduced by several lovely women, themselves often involved in the crime that starts Hammer on his own criminal rampage. The law-enforcement authorities are always a step behind in their own search for the killer and seem never to take notice of the staggering number of notches on Hammer's own gun. Mr. Redman, obviously a connoisseur of the old-fashioned type of detective story, is indignant at this state of affairs:

> Detection, in the true sense of the word has been bred almost out of existence; while crime, on the other hand has become dominant. Stupidity and brutality have replaced intelligence. Salacity has supplemented ingenuity. Probability is flouted, credibility scorned, absurdity honored. A routine narrative-pattern has been developed in which sadism, exhibitionism, sexual intercourse, and murder recur at regular intervals, while homosexuality, flagellation, or some other attractive perversion occasionally adds zest to the whole.

Few physicians count themselves literary critics, although many of them are readers of crime fiction. In any case, literary merit alone can hardly be expected to make a detective story into a best seller. On the other hand, the Spillane reader, if at all thoughtful, will miss the deft development and resemblance to reality characteristic of many detective stories published before the Hammett–Chandler–Spillane era. He may dismiss the success of Spillane's efforts on the ground that the public is seeking escape fiction. But is this the whole truth? All fiction provides the reader with temporary escape, but few fictional writings are as undisguisedly sensual and psychopathologically sanguinary as Spillane's. There seems to be something more involved than the desire to escape everyday routine. The past few centuries have seen man, in Western Europe and the New World at least, put forth heroic efforts to protect himself, in his everyday life, from brutality and bloodshed. The success of these efforts now seems to be disagreeable to some segments of society, at least to the extent that millions of readers

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*Redman, B. R. Decline and fall of the Whodunit. *The Saturday Review* 35:8-9 and 31-32 (May 31), 1952.

enjoy the fruits of the Spillane pen. All this may be just as well if such writings provide innocuous gratification for those who, consciously or otherwise, feel a need for personal contact with brutal, bloody and illicit conduct. With a new Spillane at hand, one can settle comfortably in an armchair and vicariously share Hammer's amusements without running the risk of suffering the bodily injury that direct involvement would certainly entail. But how innocuous is this gratification to the immature, but not necessarily juvenile, reader?

What, if anything, should be done about this startling development? Should legislation be passed to control it? Even if it could be justified such a move might merely accelerate the sale of these orgiastic works. Possibly, a new chapter in the psychopathology of modern life is in the making. In any event it is strong medicine Spillane dispenses, perhaps a poison; and perhaps society needs an antidote.

406 Heart Hospital, University of Minnesota

CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C. CABOT

BENJAMIN CASTLEMAN, M.D., *Editor*

VIRGINIA W. TOWNE, *Assistant Editor*

CASE 38371

PRESENTATION OF CASE

First admission. A fifty-six-year-old woman entered the hospital because of paralysis of the right side.

Fifteen months before admission she had an episode of severe dyspnea, cyanosis and semicoma, allegedly due to auricular fibrillation; since then she had been receiving digitalis, ammonium chloride, mercurial diuretics and a low-sodium diet. Three months prior to entry she had an attack of paroxysmal nocturnal dyspnea, followed by six more attacks. Fifteen hours before admission she was awakened by acute dyspnea, which persisted for six hours. Twelve hours later she suddenly stopped talking, walked a few feet and just managed to throw herself onto a bed. It was noted that she dragged her right foot, was unable to move her right arm and was unable to speak.

At the age of twenty-seven she had had an illness characterized by sore legs, for which she was in bed for several months. The patient had been known to have hypertension for ten years.

Physical examination revealed a somewhat agitated, mildly cyanotic, dyspneic woman, who was able to speak only a few words. The neck veins were slightly distended. There were moist rales at both bases posteriorly. The heart was considerably enlarged, with the point of maximum impulse at the anterior axillary line in the fifth intercostal space. The rhythm was grossly irregular. There was a faint, blowing, apical systolic murmur, and a distinct diastolic third heart sound heard along the left sternal border. There was mild pitting edema of the ankles. There was weakness of the right facial nerve and of the right hand and leg; all deep tendon reflexes were present and equal.

The temperature was 101°F., the pulse 110 and irregular, and the respirations 24. The blood pressure was 240 systolic, 140 diastolic.

Examination of the blood showed a hemoglobin of 14 gm. and a white-cell count of 12,800, with 81 per cent neutrophils. The urine had a specific gravity of 1.018 and gave a +++ reaction for albumin. Roentgenograms of the chest revealed enlargement of the heart in the region of the left auricle and ventricle (Fig. 1). An electrocardiogram disclosed auricular fibrillation with a ventricular rate of 90, a QRS interval of 0.08 second and high voltage in the precordial leads. The ST segments were depressed in Leads 1, 2, AFL, AVF, V_4 and V_5 and elevated in Lead AVR.

The patient responded well to morphine, aminophylline, Cedilanid, mercurial diuretics and oxygen. She rapidly regained strength in the limbs but continued to have some difficulty with her speech. She was discharged after fifteen days to take digitalis, ammonium chloride and a low-salt diet. The blood pressure in the hospital had varied between 260 systolic, 150 diastolic, and 160 systolic, 100 diastolic.

Second admission (twenty-one months later). During the interval the patient had been on the above therapeutic regimen, and periodic oxygen and mercurial diuretics. During this period she had led a very restricted life and had had frequent bouts of pulmonary edema and paroxysmal nocturnal dyspnea. One year prior to admission a dilatation and curettage were performed because of vaginal bleeding; the histologic diagnosis was endometrial hyperplasia. Four hours prior to entry, while walking

about the house, she quite suddenly had difficulty in breathing that became progressively worse to the point of severe dyspnea. She did not faint, and there was no chest, arm or jaw pain. Oxygen by mask and morphine intramuscularly failed to give relief.

Physical examination revealed severe dyspnea, moist generalized rales throughout both lung fields, a grossly irregular, rapid heart rate and an enlarged heart. The temperature was 101°F., and the blood pressure was 170 systolic, 90 diastolic.

She responded well to therapy, with great improvement in the dyspnea. On examination after the acute phase had passed the findings were slight cyanosis, dyspnea at rest, slight distention of the neck veins, a few moist rales at the lung bases, auricular fibrillation, moderate accentuation of the second pulmonic and marked accentuation of the first mitral sounds, a pronounced protodiastolic gallop at the base, a coarse, Grade I, apical diastolic rumble and a slightly tender, moderately enlarged liver. The blood pressure was 235 systolic, 140 diastolic.

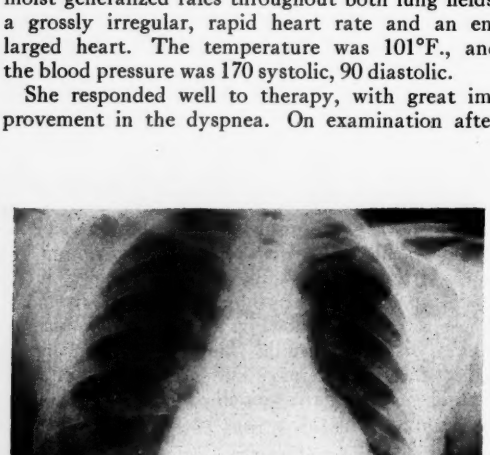

FIGURE 1.

Examination of the blood showed a hemoglobin of 18.4 gm., a hematocrit of 51 per cent and a white-cell count of 24,000. The nonprotein nitrogen, sodium, chloride, potassium and carbon dioxide were normal. An electrocardiogram revealed auricular fibrillation at a rate of 100 and intermittent left-bundle-branch block.

The patient improved markedly on therapy in the hospital, and the apical rate dropped to 84. During her stay in the hospital she had another episode of vaginal bleeding; adenocarcinoma arising in an endometrial polyp was found on biopsy, and she received 3000 r by intracavitary radium application on two occasions two weeks apart.

Third admission (ten months later). In the interval she received digitalis, a salt-free diet, mercurial diuretics and for a time Protoveratrine. She led a bed-to-chair existence, had orthopnea requiring three pillows for relief, no ankle edema or chest pain, and dyspnea at rest only if mercurial diuretics were withheld for more than four days. She was followed closely in the hypertension clinic; she entered the hospital for cardiac-catheterization studies, which revealed no pulmonary hypertension. After 0.12 mg. of the Protoveratrine had been given intravenously, a significant fall in systemic blood pressure, pulse, and cardiac output was noted. Nine months before admission she had the onset of "spells" described as a "bouncing of her heart," which occurred approximately twice a week, usually just about the time she was falling asleep; there was no pain, but she became frightened and began to perspire. Three months before admission she was admitted to the emergency ward in acute pulmonary edema and responded to therapy quite rapidly. While in the hospital she had a number of "spells" in which she became cold, clammy and short of breath, complained of a strange feeling over the precordium and felt that she was going to faint. Examination during one of these demonstrated a regular apical heart rate at 200; after carotid pressure the rate was 96, and there was subjective improvement. Quinidine sulfate was added to the treatment. Prior to discharge she was able to lie flat without dyspnea; the lungs were clear, and the pulse 64 and irregular.

She was seen once after discharge and was apparently doing well. On the evening prior to entry she allegedly passed a large gush of bright-red blood by rectum. On the day of admission she experienced what her family described as a "heart attack." After this she was confused, suspicious and somewhat combative and refused to take any of the medications.

Physical examination revealed a confused, uncooperative woman whose speech was slurred and hesitant. Neurologic examination was difficult to evaluate because of the lack of co-operation and the inability of the patient to comprehend; the abdominal and deep tendon reflexes in the lower extremities were absent. There was diffuse abdominal tenderness but no masses. Rectal examination revealed only feces mixed with blood on the examining finger. Pelvic examinations were negative except for some slight thickening in the region of the left broad ligament. There was no evidence

of cardiac failure, and the heart findings were as before.

The hemoglobin was 13.5 gm. per 100 cc. A gastrointestinal series and barium-enema and sigmoidoscopic examinations were negative.

Within six days she was quite alert and oriented. She was discharged on the eighth day.

Final admission (one month later, at sixty years of age). While at home she took digitalis and quinidine. There was apparently no change in the symptomatology until five days prior to entry, after a visit to the surgical clinic, where proctoscopic examination revealed a mucous-membrane abrasion just above the hemorrhoidal area. Thereafter she felt tired and upset and again showed elements of paranoic behavior. Three days prior to entry she began to have diarrhea, with three or four loose, dark stools a day, and vomiting; on several occasions the vomitus contained dark-red blood. During the twenty-four hours before admission she had three attacks of high substernal choking sensation lasting for a few minutes to an hour and associated with a feeling of chilliness and nausea. Shortly before admission she had the sudden onset of dizziness, faintness and shortness of breath and apparently fell over.

Physical examination revealed a well nourished, markedly cyanotic woman who was cold, sweaty and dyspneic and had vague chest and abdominal pain. The neck veins were not distended. The lungs were clear. The heart rhythm was regular at a rate of 140. The heart was enlarged, with the left border of dullness at the anterior axillary line. There was a protodiastolic gallop and an apical systolic murmur. The pulmonic second sound was greater than the apical. The abdomen was soft. There was alleged diffuse abdominal tenderness; no enlarged organs or definite masses could be made out, and peristalsis was normal. There was no ankle edema. Pelvic examination was as before. The carotid and brachial pulses were present, but the femoral pulses could not be felt; the lower extremities were cold and cyanotic. The deep tendon reflexes were absent in the lower extremities.

The temperature was 101°F.; the blood pressure was 240 systolic, 150 diastolic.

The urine was normal. Examination of the blood showed a hemoglobin of 13.5 gm. per 100 cc. and a white-cell count of 14,800, with 88 per cent neutrophils. The nonprotein nitrogen was 66 mg. per 100 cc., and the serum sodium 140.7 milliequiv. and the chloride 96 milliequiv. per liter. The stool and vomitus both gave a ++++ guaiac reaction. An electrocardiogram revealed auricular fibrillation and a ventricular rate of 160.

The pulse rate slowed to 108 spontaneously after one or two hours without specific therapy; the patient improved somewhat, but the cyanosis persisted. Twenty hours after admission she again became severely dyspneic and deeply cyanotic. The heart rate was 68 and irregular, and the blood pressure was unobtainable. The carotid pulse could be felt, but the femoral and brachial pulses could not. She complained of generalized pain, and the abdomen was rigid. She was given oxygen by mask but remained deeply cyanotic and dyspneic; the pulse and respirations gradually slowed, and she died twenty-four hours after admission.

Differential Diagnosis

Dr. David Littmann*: It is difficult to fit this long and complicated case into a simple form. This woman had had, twenty-seven years before admission, an attack of painful joints, which was probably rheumatic fever and for which she remained in bed for several months. Then, at the age of forty-six, she was discovered to have hypertension, which in view of subsequent events could not have been very severe and was not particularly symptomatic. Eight years later auricular fibrillation, bouts of dyspnea and cyanosis developed, and at the age of fifty-six she began to have frequent attacks of extensive paroxysmal nocturnal dyspnea. She was admitted to the hospital after a cerebrovascular accident and apparently was in cardiac failure. At that time she had auricular fibrillation, physical findings suggestive of mitral stenosis or insufficiency, or both, a blood pressure of 240 systolic, 140 diastolic, a fairly well concentrated urine giving a +++ test for albumin and x-ray evidence of an enlarged left auricle and ventricle.

May I see the x-ray films?

Dr. Chiu-Chen Wang: In the first examination of the chest done five years before entry the heart is somewhat enlarged to the left. There is slight elevation of the left main bronchus and posterior displacement of the barium-filled esophagus, suggesting enlargement of the left auricle. The series of examinations from that time to the time of the last admission demonstrate slight progression of cardiac enlargement, chiefly in the region of the left ventricle and left auricle. There is no fluid in either costophrenic angle. The pulmonary vessels appear somewhat engorged on both sides (Fig. 1). There is no evidence of heart failure in any film.

Dr. Littmann: The electrocardiogram at that time showed auricular fibrillation, changes that suggested the effect of digitalis and high voltage in the precordial leads. It is not clear whether the high voltage involved the inner or outer leads; this may have represented ventricular hypertrophy.

The patient was treated and recovered rather promptly. It is interesting that the cerebrovascular accident appeared abruptly after an attack of extensive pulmonary edema and that the symptoms apparently had begun to clear by the time the pa-

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tient reached the hospital. The physical findings had cleared almost entirely by the time she was discharged. The onset suggests to me a cerebral embolus rather than a thrombus or a hemorrhage. Although symptoms with cerebral hemorrhage can occur very acutely, they are not likely to clear up quite so well. With cerebral thrombosis the manifestations ordinarily take longer to develop.

During the second admission there was evidence of mitral stenosis — at least, a rumbling mitral diastolic murmur was heard. There was a somewhat large liver and considerable hypertension. Of interest, too, was the hemoglobin of 18.2 gm. per 100 cc., with a hematocrit to go with it — and a high white-cell count. At that time the electrocardiogram showed, in addition to the auricular fibrillation, intermittent left-bundle-branch block. Left-bundle-branch block may, of course, occur with hypertrophy of the left ventricle; it is not common with disease of the right side of the heart.

During the interval between the second and third admissions, cardiac-catheterization studies were done. That these demonstrated no pulmonary hypertension makes me unhappy. If the trouble was primarily due to severe, long-standing hypertension some pulmonary hypertension would be expected; if it was due to mitral stenosis pulmonary hypertension would also be expected. The absence of pulmonary hypertension on catheter examination suggests at least that whatever caused the clinical pulmonary hypertension must have been intermittent.

I do not quite know how to explain the bleeding by rectum except as a manifestation of radiation proctitis. Dr. Richard Warren, whom I asked whether radium could have such an effect, said it might. At least, no mention was made of hemorrhoids, and subsequent examination by proctoscope showed nothing. The third admission was for a neurologic difficulty. At that time the patient was not in cardiac failure, and the cardiac findings were as before. The hemoglobin had fallen to 13.5 gm. from the 18 gm. noted before, perhaps as the result of the bleeding. She improved and went home in six days.

The terminal episode occurred a month later. For the first time she had a high substernal choking sensation lasting from a few minutes to an hour, associated with a feeling of chilliness and nausea. She was markedly cyanotic, cold, sweaty and dyspneic and had chest and belly pain, a soft abdomen, a fever and a high white-cell count. The neck veins were not distended; they had been on previous occasions. The blood pressure was 240 systolic, 150 diastolic. Perhaps something happened to the aorta, probably at the bifurcation. It is not clear why the urine should have been normal. One detail that was not immediately explained is the loss of the brachial pulses; however, the patient was moribund, and the blood pressure was unobtainable.

The hypertension I find very difficult to settle. There are not many types of hypertension, other than the essential type, that last as long as fifteen years. The intermittency of the attacks of dyspnea, if they were indeed due to hypertension, makes me think of the type of hypertension occurring with a pheochromocytoma. I have no way of ruling out pheochromocytoma except that it is unlikely to last that long. The attacks may not have been due to hypertension since it seems unlikely that hypertension causing this degree of cardiac symptoms would limit itself to left-sided failure without congestion or right-sided failure. Mitral disease does not fit very well either. Rheumatic fever, when it occurs in adults, is less likely to produce the striking changes seen when it develops in children. Although mitral stenosis of high order may be present with almost no mitral murmurs, this usually occurs as a terminal event. This woman was observed for four years and apparently only had a Grade I diastolic murmur, so I suspect she did not have high-grade mitral stenosis. She did, however, fibrillate, so I am almost certain she had embolic disease arising in the left auricle.

One can imagine a thrombus of the left auricle, possibly a ball-valve or pedunculated thrombus that from time to time occluded the mitral valve and caused the striking attacks of dyspnea and pulmonary edema; yet, conceivably at a time when the thrombus was not occluding the valve, the pulmonary pressure would not have been great.

The hypertension bothers me, and I should like to tie all the findings together. The only way I can do that is to assume that there was an embolism of one or both of the kidneys with a large amount of nonfunctioning renal tissue that could have produced or exaggerated pre-existing hypertension — this, in addition to mitral stenosis and multiple peripheral emboli. The terminal episode almost certainly was a large embolus to the bifurcation of the aorta, resulting in the loss of pulsation of the femoral vessels, with cyanosis and coldness of the legs. She had severe abdominal symptoms — a rigid belly — before death so I think there may have been an embolus of the mesentery. One cannot blame all the symptoms on one long embolus because the urine was normal. I suspect that there was a series of emboli, rather than one large one extending from the bifurcation of the aorta to the celiac axis. On a statistical basis, she may have had a great many more emboli than I have mentioned — to the spleen and possibly to the coronary system to account for the chest pain before death. She probably had some pulmonary infarcts; patients with rheumatic disease who die usually have pulmonary infarcts. I doubt whether she had any of the other causes for hypertension; there was nothing in the history to suggest Cushing's syn-

drome, polycystic kidneys, nephritis or pyelonephritis. I am concerned about an omission that may have been inadvertent. An intravenous pyelogram might have helped me to decide about embolized kidneys.

Dr. Wang: In an intravenous pyelogram done a year before death, the kidneys appeared to be within normal limits. The spleen was enlarged.

Dr. Littmann: I gather that the possibility of extensive embolic disease had not concerned the medical service because there was no record of anticoagulant therapy. One should consider the possibility of subacute bacterial endocarditis. She did have fever each time she came in, but nothing else to support that diagnosis. Another possibility one should consider is dissecting aneurysm, but in the absence of pain I cannot make that diagnosis. I suppose there may have been some adenocarcinoma of the uterus and some radiation proctitis. During the last two or three years of life, when she lived essentially a bed-to-chair existence, venous thrombosis of the legs may well have developed. This would account for the subsequent emboli to the lungs.

Dr. James H. Currens: Would it help you to know that this woman had some twelve or fifteen episodes, for which the fire department had to be called? This information was collected by the referring physician and was not known to us before she died.

Dr. Littmann: Does that mean she had more attacks than we suspected?

Dr. Currens: Yes.

A Physician: She made the statement the day before she died, "Why do the doctors always make me sit up when I have these attacks? I feel much better when I lie down."

Dr. Littmann: That, too, suggests the possibility of a ball-valve thrombus; the left auricle is a little above and behind the left ventricle so that the valve orifice is above the line of the thrombus when the patient is lying down.

Clinical Diagnoses

Hypertensive heart disease.
Probably rheumatic heart disease, with mitral stenosis.
Dissecting aortic aneurysm.

Dr. Littmann's Diagnoses

Rheumatic heart disease, with mitral stenosis.
Ball-valve thrombus, left auricle.
Massive embolus to bifurcation of aorta.
Emboli to kidneys, ?spleen and ?coronary arteries.
?Radiation proctitis.

Anatomical Diagnoses

Rheumatic heart disease, with mitral stenosis.
Ball-valve thrombus, left auricle.
Massive embolus to bifurcation of aorta.
Infarction of colon and ileum, recent; of kidneys and spleen, old.

Pathological Discussion

Dr. Benjamin Castleman: The autopsy showed a moderately enlarged heart, weighing 420 gm. — a mild hypertrophy of the left ventricle suggesting slight hypertension. The left auricle was enlarged and, as predicted by Dr. Littmann, contained a large ball-valve thrombus, which was free in the auricular cavity. It could be moved around. There was a mild degree of mitral stenosis; the valve admitted one finger easily. The ball-valve thrombus was laminated and organized and had a smooth surface. The layering of the thrombus represents added thrombus over the years. There was a saddle embolus at the bifurcation of the aorta that apparently was recent; undoubtedly, some of the thrombus on top of the ball-valve thrombus broke off and lodged in the abdominal aorta, below the mouth of the renal artery. Although no embolus was found in the superior mesenteric artery, there may have been small occlusions because the ascending colon and part of the ileum were infarcted and filled with bloody fluid, which was the cause of the positive guaiac reaction on the stool. We found evidence of old infarcts in both kidneys; the right kidney at the time of autopsy was shrunken, weighing only 80 gm. I did not know that there was a pyelogram; with that as evidence, I believe the infarct must have occurred after that film was taken. I did not realize that so much reduction in the size of a kidney could occur in such a short period. There was also an old infarct in the spleen.

The cause of the bleeding, before the infarct of the bowel was present, was probably an adenomatous polyp that was found in the sigmoid. There was no evidence of radiation change and no evidence of residual tumor; the tumor in the endometrium had been of very low grade of malignancy and was entirely cured.

Dr. Currens: One finding on auscultation that was misleading and confusing to me at least was the rather loud third heart sound that this patient manifested during the year and a half that I observed her; at least, it occurred quite early in diastole, was of medium frequency and was best heard 2 or 3 cm. to the left of the left border of the sternum in the fourth interspace, although it was easily audible at the apex. Perhaps in retrospect it was an opening snap of the mitral valve. Certainly, there was clinically more evidence of hypertensive heart disease than of rheumatic heart disease; a slight diastolic rumbling murmur and apical third heart sound are seen in association with dilatation of the left ventricle. I should like to compliment Dr. Littmann on his astute analysis.

Dr. Castleman: What is your opinion about asking the surgeons to open up the left auricle to remove such a ball-valve thrombus?

DR. LITTMANN: I do not think the ones I have seen could be removed.

DR. CURRENS: Through the auricle you mean? The surgeons are usually reluctant to open any larger hole in the atrium than the base of the auricular appendage.

DR. WARREN: What was the measurement of the thrombus?

DR. CASTLEMAN: Six by 5 by 3.5 cm.

DR. CURRENS: Drs. P. A. Ongley and L. D. Arias have reviewed the phonocardiogram, which they recorded six months before this patient's death. It was of considerable interest. A characteristic third heart sound was visible in most cycles and was synchronous with the rapid inflow phase of the apex cardiogram. This sound although early in diastole was too late in the cycle for an opening snap of the mitral valve. In a few cycles a peculiar third sound was visible slightly later in diastole and of much smaller amplitude, coincident with a much more gradual inflow curve in the apex cardiogram. They have postulated partial obstruction of the mitral orifice during certain periods of diastole by the ball-valve thrombus to account for the variation of this third heart sound.

CASE 38372

PRESENTATION OF CASE

A thirty-four-year-old man was admitted to the hospital because of pain in the left side of the chest.

Two months before admission the patient first noted an ache in the left axilla while sweeping a floor. This ache was worse on deep breathing, coughing or sudden movement. About one month prior to admission he had a mild chill, fever with a temperature ranging from 100 to 101°F., and a mild cough productive of a small amount of whitish, mucoid sputum. This illness was short lasting, but thereafter the pain persisted and gradually became more severe but remained pleuritic. He next noted a very tender spot over a rib in the left axilla. He believed that a low-grade fever had been present intermittently. There had been no hemoptysis, hoarseness, weight loss or exposure to tuberculosis.

Physical examination showed a well nourished man in mild distress complaining of pleuritic pain in the right side of the chest. A tender soft-tissue fullness, 5 by 2 cm., was felt in the midaxilla over the left sixth rib. A soft patchy friction rub of leathery quality was heard over the left-lung base posteriorly and at the left posterior and midaxillary line. Otherwise, the chest was clear to percussion and auscultation. The remainder of the physical examination was noncontributory.

The temperature was 100°F., the pulse 80, and the respirations 20. The blood pressure was 100 systolic, 60 diastolic.

Urinalysis was negative. Examination of the blood revealed a white-cell count of 8800, with 68 per cent neutrophils, and a hemoglobin of 16 gm. The nonprotein nitrogen was 19 mg., the calcium 10 mg., the phosphorus 3.7 mg., the alkaline phosphatase 3.3 units, and the total protein 7.48 gm. per 100 cc., with a normal albumin-globulin ratio. The sedimentation rate was 12 mm. per hour. Roentgenograms of the chest demonstrated a destructive process in the left sixth rib in the axillary line, involving the entire thickness of the rib over a distance of about 3 cm., with a soft-tissue

FIGURE 1. *Roentgenogram of the Chest. Arrows point to soft-tissue mass.*

mass both inside and outside the chest cage (Fig. 1). There was a suggestion of increase in the fine mottled markings throughout both lung fields, most pronounced peripherally, and a small amount of fluid in the left costophrenic angle as well as some adherence of the left leaf of the diaphragm. Intravenous pyelograms showed a double renal pelvis and double ureter on the left; no other abnormality of the upper urinary tract was demonstrable. Gastrointestinal series, barium-enema examinations and films of the lumbosacral spine and pelvis showed no abnormalities.

On the eleventh hospital day an operation was performed.

Differential Diagnosis

Dr. Ronald C. Sniffen*: In brief, this thirty-four-year-old man had acquired, without trauma, a destructive lesion in the left sixth rib accompanied by a soft-tissue mass in the region. Apparently, the process had led to pleural irritation and a small amount of fluid in the pleural cavity. Pleural pain and tenderness were the only subjective symptoms. Physical examination demonstrated a nonpulsating mass in the soft tissue over the sixth rib and confirmed the impression of pleuritis given in the history.

Obviously, the roentgenographic findings are of the utmost importance. What had the process done to the rib? Was it entirely osteolytic? What was its contour? Was there a periosteal reaction or change in the neighboring bone? Finally, were there significant collateral findings?

Dr. Stanley M. Wyman: We see the fine rather granular mottling in the films of the chest that appears rather diffusely distributed and is unaccompanied by appreciable lymph-node enlargement. There is a tiny quantity of fluid in the left pleural cavity that is best seen posteriorly. The destructive lesion in the left sixth rib, described in the protocol, shows no new-bone formation, periosteal reaction or ray formation. The Bucky films best demonstrate the accompanying swelling about the rib both medially and laterally. The bones are otherwise well preserved, and the spleen appears well within normal limits in size; no other lesions are seen.

Dr. Sniffen: Is there any evidence of lymphatic involvement in the lung?

Dr. Wyman: No; I do not think there is any significant enlargement of the linear shadows in the lungs to suggest characteristic lymphatic involvement.

Dr. Sniffen: I am overwhelmed by negative findings. The patient did not feel ill and had not lost weight; the laboratory tests were entirely negative, and x-ray examination demonstrated no abnormality except the fine mottling throughout the lung fields — actually, that finding is very disturbing. In every patient's history there are at least a few worrisome interjections, which may guide one's train of thought. They may be abruptly discarded or carefully included to bolster a particular condition. From the history, trauma can be dismissed as a causative factor. One month before admission the patient had a chill with fever and a cough. I do not consider this episode important principally because of its short duration, the unexciting character of the sputum and the lack of relation to the chest pain. Yet there was a suggestion of subsequent intermittent fever, and the temperature was slightly elevated at the time of admission. I do not believe that the lesion in the rib was the result of an acute pyogenic infection: the pleural pain preceded the local tenderness; the location of the lesion is against it; there was no change in the overlying skin; and the regional subcutaneous lymph nodes were not enlarged. Furthermore, leukocytosis was absent, and the sedimentation rate was normal.

Tuberculous osteomyelitis is a possibility, but the process seemed a little rapid and painful for this disease. In attempting to draw the findings together, I cannot believe that there was disseminated tuberculosis in the lungs. Certainly, tuberculous osteomyelitis may exist without another demonstrable focus of disease or laboratory findings indicating infection. However, tuberculosis is unusual in a rib and is not entirely osteolytic, as this lesion appeared to be.

The location and x-ray appearance are against syphilis, and surely actinomycosis of a rib would be secondary to a large pulmonary lesion. From the x-ray evidence only, echinococcus disease might be considered, but the cyst usually grows more slowly and is painless. The history does not support this diagnosis, and apparently there was no eosinophilia; skin tests were not mentioned.

There was no clinical or laboratory evidence of metabolic bone disease. The serum calcium, phosphorus and alkaline phosphatase were normal, and the kidney function was unimpaired as far as it was investigated. No change was demonstrable in the rest of the skeleton.

Of the xanthomatoses of bone, I should consider seriously only eosinophilic granuloma. This condition often produces a solitary lesion in a rib of fairly abrupt onset. There is pain, tenderness and swelling, and bone destruction reaches a maximum in a few weeks. Usually, the bone is rarefied, and the shell is expanded, but may be totally destroyed.

Monostotic fibrous dysplasia is common in a rib, but the x-ray appearance is different and this patient's symptoms were too definite for that condition.

If the patient had a tumor, I believe that it must have been malignant. Having made that statement, one must decide whether the tumor was primary or metastatic. Again, the findings in the lungs come under scrutiny. Was the fine granular mottling an indication of metastatic tumor, and, if so, was it part of a generalized dissemination of tumor or was it secondary to the tumor in the rib? In a somewhat uncertain tone, I shall say that the lungs did not contain tumor and furthermore probably had nothing to do with the immediate problem. I should expect a patient with metastatic tumor in the lungs visible in the films as diffuse mottling, and therefore presumably spreading via the lymphatics, to show progressive incapacitation, with weight loss, dyspnea, cough, cyanosis and hemoptysis. The patient may have had a solitary metastatic tumor in the rib, and the x-ray appearance of the lesion is consistent with this diagnosis. Yet one is not

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justified in making such a diagnosis without at least a clue to the location of the primary tumor. In this regard the kidneys, prostate, stomach, lungs and thyroid gland should be examined as thoroughly as is practical. The unobtrusive growth of cancer of the pancreas and difficulty in examining the region make this disease notoriously treacherous.

It is often difficult to differentiate the various malignant tumors arising in bone by any means short of microscopical examination. Even then the pathologist sometimes resorts to masterful hedging, a skill at which he should be highly proficient and without peer, the roentgenologist excepted. Like the drowning man, one must clutch at straws. The patient's age does not help me in the least. It has influenced me in dismissing certain diagnoses, but in the end I shall disregard it.

Osteogenic sarcoma is uncommon in a rib, and the appearance of the x-ray film in the case under discussion is not consistent with this tumor in its usual form. I should be happier if I could forget the osteolytic sarcoma that does not produce ray formations.

Chondrosarcoma may destroy bone in this fashion. In early lesions the tumor is often situated outside the bone proper, and the marrow is not involved. It may have a lobulated contour, and frequently the histology is not uniform and calcification takes place so that blotchy areas of increased density are seen in the x-ray film. Chondrosarcoma may arise in a chondroma, but the patient had not noticed swelling in the rib before the rapid development of the present lesion.

Lymphoma cannot be dismissed despite the fact that this was a solitary lesion. Conceivably, there was diffuse pulmonary involvement, but the possibility seems highly unlikely. There was no apparent lymph-node enlargement or splenomegaly and no aberration in the blood count in the form of either leukemia or anemia. Solitary lesions of bone in lymphoma are distinctly uncommon and usually arise as reticulum-cell sarcoma in a long bone of an extremity.

Myeloma is common in the ribs and does not stimulate new-bone formation; pain may be a feature of the disease. In general, it is unusual for myeloma to extend beyond the cortex, and most frequently the bone is diffusely mottled and the break is not clean, but develops through a widened and rarefied area. Myeloma seldom grows to this size without appearing in other bones. Furthermore, the patient was young for the disease. Bence–Jones proteinuria was not mentioned; there was no indication of renal disease, and the serum protein was not elevated.

It seems very likely to me that this patient had Ewing's tumor, and the pain, swelling and slight elevation of temperature are consistent with this diagnosis. Yet the x-ray appearance of the lesion is not characteristic. The tumor had destroyed the cortex, and classically this event stimulates the production of layers of periosteal new-bone formation. Unfortunately, there are many exceptions to this textbook picture. Ewing's tumor usually occurs at an earlier age and is most common in the shaft of the long tubular bones and in the pelvic bones.

In full anticipation of a curve ball or a looper crossing my blind spot, I shall single out two conditions as the best possibilities — namely, Ewing's tumor and eosinophilic granuloma. Admittedly the patient was rather old for either of these conditions. Nevertheless, my first choice is eosinophilic granuloma because the glove seems to fit: in brief, a rapidly developing solitary lesion in a rib accompanied by pain, tenderness, slight fever and a mass that on x-ray examination is seen as an osteolytic lesion with soft-tissue swelling.

Clinical Diagnosis

Inflammatory tumor of sixth rib.

Dr. Sniffen's Diagnosis

Eosinophilic granuloma of rib.

Anatomical Diagnosis

Eosinophilic granuloma of rib.

Pathological Discussion

Dr. David Kahn: Dr. Sniffen seems to have had no trouble in knocking our best pitch clear out of the park. Preoperatively there was no great unanimity of opinion about the diagnosis; primary malignant bone tumor, metastatic cancer and inflammatory process were considered as possibilities, with the last condition considered the most likely. However, because primary malignant bone tumor was still a strong possibility, the chest-wall tumor was resected en bloc, including the entire sixth rib along with short segments of the fifth and seventh ribs adjacent to the tumor; when the chest cavity

was open, it was seen that the pleura was covered with fibrin and gave evidence of inflammation, although the underlying lung substance appeared to be soft and showed no abnormality. When we examined the specimen in the laboratory we found that there was a mass measuring 5.5 by 2 by 1.5 cm. occupying and replacing the midportion of the sixth rib. A thin, expanded remainder of cortical bone of the rib surrounded the anterior, superior and inferior portions of this enlargement; posteriorly, there was an area in which cortex could not be made out, and the mass extended posteriorly and was adherent to a small piece of attached parietal pleura. The tumor was soft and somewhat mushy and was dark yellow. There was abnormal mobility of the rib at the involved region. The adjacent ribs were not remarkable. Histologically, a large portion of the mass was necrotic; however, there were well preserved areas that showed typical eosinophilic granuloma. In these areas there were broad bands of mature eosinophils, with small focal areas of mononuclear phagocytes or histiocytes scattered throughout. Almost all the cancellous bone of the rib in the involved area was replaced. The granuloma extended to, but not through, the parietal pleura.

Four months after operation, the patient was asymptomatic; the physical examination was negative, and the radiologic changes in the lung parenchyma were still present. I suppose we can assume that the pleural friction rub and small amount of pleural fluid were secondary to irritation of the parietal pleura by the tumor mass.

Addendum

Dr. J. Gordon Scannell: There is little to add to Dr. Sniffen's excellent analysis of the problem. Those of us who were charged with the clinical management of this patient took refuge in the term "inflammatory tumor." Believing that the best way to establish the diagnosis was by radical-excision biopsy, we proceeded on the basis that tumor had not been excluded. One can employ this radical approach in an expendable bone such as rib and yet produce surprisingly little functional damage to the chest wall. As surgeons we have been impressed by the dismal course of patients in whom a rib tumor is actually cut into at the time of its removal, especially if malignant.

Dr. R. S. Shaw and I have recently reviewed the experience at this hospital with solitary eosinophilic granuloma of rib. This represents the fourth such case. The association of severe pain disproportionate to the radiologic findings was strikingly constant. The patients were all of the young-adult age group. All did well after excision of the involved rib or liberal portions thereof.

I am chagrined that we did not obtain a biopsy of the lung at the time of rib resection. The pleural surface showed considerable fibrinous thickening, as Dr. Kahn has stated.

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UNFINISHED BUSINESS

THE relations between physician and patient, a cause of constant concern within the profession, will remain always as unfinished business on the agenda of medical affairs. They constitute, in fact, a permanent practical problem as old as the history of medicine itself — and yet new with each increment of recruits to medical practice.

The question may be asked, What has been the nature of these relations in the past, what is it now, and how did it come to be that way? Was it as uniformly good in the old days as fond but unreliable recollection would have one believe, and is it as universally poor today as various reports might lead one to assume? Have doctor-patient relations really deteriorated, and if so, has this deterioration been greater than that which pertains to other co-operative adventures in gregarious living, or is the present situation simply a sharing of the result, with all other forms of human relations, of excessive competition, mutual suspicion and general insecurity?

The answer is suggested by Roberts[1] in *The Cost of Health.*

> The counsel given by the writer of *Ecclesiasticus* to honour a physician and the designation of medicine as a noble and learned profession may persuade us that the doctor has always been held in high honour. This view is mistaken. The dubious parentage and the inherent mystery of the medical art prevented its exponents from being accorded due recognition until comparatively recent times. Even today the attitude of the public is mercurial and unreliable; it fluctuates, according to circumstances, between extremes of emotional gratitude and hostile criticism.

And yet despite all the ills from which human relations still suffer, the slow growth of social consciousness has nevertheless given a better goal toward which to strive than has ever been man's lot before.

True, the faithful family doctor of bygone days is considered by many to be medicine's bright tradition — although he has his counterpart in the present — but it is a question whether, on the whole, personal relations were any better formerly than now, and certainly the quality of medical care is infinitely better now than it was formerly. More has become available and more is expected, and in the delivery of this complicated and unavoidably expensive service a certain impersonality has become an inevitable part of the picture. For the patient today may be cured of a once fatal illness by an expert whose name he didn't quite catch, instead of dying with his old family doctor sitting loyally at the bedside.

These doctor-patient relations, whether or not they have deteriorated, have nevertheless been considered as sufficiently uncertain to warrant having a "psychologic" study of them made for the California and Alameda County medical associations.[2] In this study, whose final report was submitted to the two organizations in 1950, much interesting information was obtained from tape-

recorded "depth" interviews with a variety of physicians and of patients.

In the final analysis the conclusions to be drawn from the report are that the composite physician, a somewhat temperamental and insecure individualist, mingles in his make-up idealism, secretiveness, a sense of importance, a love of the *feeling*, at least, of power, and a fear of that socialization of his activities that might tend to destroy his cherished individualism.

His patients resent most of these qualities in him — except the idealism, of which they would welcome still more, even to the point of expecting him to labor unceasingly in their behalf to his own detriment. Many of them, with their minds on these priestly qualities, believe that they are underserved and overcharged by a profession that thinks too highly of itself and not highly enough of its public. Unfortunately there are always enough individual members of the medical profession whose behavior seems to justify the indictment.

The solution of these problems lies in the establishment of a base for mutual confidence that must be initiated by the physicians themselves. They are the ones whose motives and whose methods are misunderstood by the less well informed public whom they serve, and they owe to that public on which they depend for their professional existence a clear and satisfactory explanation of the ways in which they function. The mystery in medicine has been one of its greatest liabilities; the pedestal on which the doctor has been so willing to be placed has given him an isolation that has never been in his own best interest.

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THE NATIONAL MEDICAL LIBRARY

The "national" medical library, so-called, again has taken a step forward toward its ultimate goal as a library for all the people of the United States.

An official directive has been issued announcing the appointment of Lieutenant Colonel Frank B. Rogers, M.C., U. S. Army, as Director of the recently established Armed Forces Medical Library. Colonel Rogers was director of the Army Medical Library since October, 1949, and is now continued in office under the new administrative reorganization.

It is unfortunate that a definite term of office is not specified in the notice, for continuity in office is essential for the best management of such a large facility of the Government.

The Director of the Library is responsible for administrative policies and over-all supervision. The management and functioning of the Library is entrusted to a professional librarian protected by Civil Service regulations. The present incumbent, Mr. Kanardy Taylor, is a competent, well qualified, experienced librarian.

In 1864 Dr. John S. Billings assumed custody of the small collection of books, begun in 1836, and at that time called a library, and began avidly collecting medical literature, starting the library on its march to world supremacy in its particular field. Dr. James R. Chadwick, librarian of the Boston Medical Library, worked closely with Dr. Billings, and together they combed the world in the interest of both the libraries; the two libraries have continued this traditional mutual friendship since its inception in 1875.

In 1880 the accumulation of material had become so great that the famous and invaluable *Index Catalogue* was founded. A year earlier, the *Index Medicus* had been established for the purpose of providing current medical literature for all physicians. Dr. Billings was farsighted, and his fame is securely based on these two monumental works. Owing to unsurmountable handicaps, financial and functional, publication of both these outstanding bibliographic tools has ceased; their place has been taken by other methods designed to provide current medical literature for the medical and allied professions. Statistics are usually dry and uninteresting, and it is sufficient to note that the volumes number about 650,000 and that the coverage is comprehensive from the earliest times to date, in all languages. Naturally, the historical collections are superb.

Under the new organization, the Library is designated the Armed Forces Medical Library, technically under the control of the Secretary of Defense. It serves primarily the Army, Navy, Air Force and Government agencies, and secondarily it is not only

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a national but an international source for medical information. The Library at present is subject to all the vagaries of politics and appropriations. When cuts are made the Library usually feels the effects immediately. In this respect, it should be remembered that it is maintained by the people through taxation. A long step has been taken in the line for the right type of nationalization. The ideal situation would be to have the Library a self-sufficient, independent organization for the entire country.

SHERLOCK HOLMES VS. MIKE HAMMER

ELSEWHERE in this issue of the *Journal* Chapman engages in an analysis of the new formula that has been concocted for modern detective fiction by the dispensers of ersatz crime. What he finds, especially in the writings of Mickey Spillane, is "strong medicine and perhaps a poison" — of concern to the psychiatrists and probably to the medical profession in general. A specific criticism — whose import is not immediately apparent — is that the Spillane reader is denied the deft development and resemblance to reality characteristic of many detective stories published before the Hammett–Chandler–Spillane era.

Comparison is promptly invited with Sir Arthur Conan Doyle, whose adventures of Sherlock Homes can still hold their own, despite the Gay Nineties setting. One reason — and here is a point in contrast to the Spillane formula — is the physician-author's emphasis upon accomplishments of observation and reason as well as the details of the crime. There is evidence to suggest that the eminent detective was patterned upon the keenest of clinicians — some say Joseph Bell — though there is undoubtedly a significant contribution of Doyle's own clinical and logical prowess. One suspects that if he had lived in contemporary times he might well have rebelled against the paper-back trends of the 1950's and devoted his skills to the solution of real medical rather than fictionalized criminal enigmas. He was a master of observation, and he was adept at handling clues, weighing evidence and emphasizing the power of deduction as opposed to the testimony of witnesses who know the answer.

More than entertainment and vicarious release from the rules of society are to be found in the soliloquies of Dr. Holmes as he sits moodily at one side of the fireplace toward evening while the storm grows higher and louder, and the wind cries and sobs like a child in the chimney. While figuring out the solution of the Five Orange Pips, he remarks:

> The ideal reasoner would, when he had once been shown a single fact in all its bearings, deduce from it not only the chain of events which led up to it, but also the results which would follow from it. As Cuvier could correctly describe a whole animal by contemplation of a single bone, so the observer who has thoroughly understood one link in a series of incidents, should be able to state all the other ones, both before and after. We have not yet grasped the results which the reason alone can attain to.

Not writing a medical paper, Doyle did not have to annotate the three sentences of this short discussion by references to Kant, Cuvier and Francis Bacon. Yet it is no accident that those references — hallmarks of true distinction — are implicit in the products of Doyle's pen.

If Doyle bowed to the disciplines of logic he was second to none as a literary craftsman in setting the stage for acts of violence. The plot of the same story is cast:

> . . .in the latter days of September when the equinoctial gales had set in with exceptional violence. All day the wind had screamed and the rain had beaten against the windows, so that even here in the heart of great, hand made London we were forced to raise our minds for the instant from the routine of life, and to recognize the presence of those great elemental forces which shriek at mankind through the bars of his civilization like untamed beasts in a cage.

It is no failure to recognize or contemplate the great elemental forces shrieking at mankind that distinguishes Doyle from Spillane. The great difference lies in how the details of the crime are developed: to what degree they are wallowed in; and the social attitudes manifested by the storytellers and their protagonists.

To recognize only the fascination of elemental forces and the caged beast that is in every man is to exercise the mental processes of the savage. Civilized people also recognize with Chapman that "the past few centuries saw mankind, in Western Europe and the New World at least, put forth heroic efforts to protect himself, in his everyday life, from brutality and bloodshed."

To wander too far from the tested principles of Poe, Doyle and LeBlanc (Arsene Lupin) may be to stumble into a snake pit of sensationalism with more than a matter of lunacy at stake. To abandon all resemblance — except the sensuous and sensual— to reality and to flout probability, scorn credibility and honor absurdity is to think uncomfortably much like the lunatic Peakes, the pistol slayer of Eileen Fahey at Columbia University. To be sanely preoccupied with sadism, exhibitionism, flagellation and murder is to go along part way with the three teen-age boys of Ypsilanti, Michigan, who attacked a young woman walking on the street and some months later bludgeoned another to death. To delight in the execution more than the chase is to share the distorted values that impelled youths sixteen and seventeen years old to shoot down and kill a stranger walking home through a park near Brooklyn on June 26 of this year. To be sure, they thought it "chicken" to turn the sights of their gun on a man sitting nearby on a park bench.

On the whole, Doyle comes off well in any comparison with his more sensational successors; but of more importance than the academic exercise of awarding an Oscar is the serious business suggested by Chapman of evaluating the social influence of the Hammett–Chandler–Spillane school of writing. Some influence, for better or for worse, is to be expected in particular from such a gigantic dissemination of Spillane's "orgiastic work," as has occurred.

Perhaps, as Chapman suggests, such writings provide innocuous gratification for those who consciously or otherwise feel a need for personal contact with brutal, bloody and illicit conduct; but, one is asked, "how innocuous is this gratification to the immature, but not necessarily juvenile reader?"

The answer cannot be rendered, but a generation that is not accustomed to undisciplined contemplation of the vicarious delights of sadism, flagellation or some other "attractive perversion" may be pardoned if it views with misgivings the Spillane success story. Perhaps, as Chapman suggests, a new chapter in the psychopathology of American life is in the making.

A writer in Albany imputes the bronchitis of clergymen to the tight swathing of their necks in white cravats.

Boston M. & S. J., *September 15, 1852*

CORRESPONDENCE

UROBILINOGENURIA AND HEMOLYTIC JAUNDICE

To the Editor: I was much interested in the Massachusetts General Hospital Case 38192, and the ensuing discussions, which appeared in the May 8 issue of the *Journal.* The discussion by Dr. Perry J. Culver requires the following correction.

In brief, this discussion indicates that I have favored the concept that excesses of urine urobilinogen were related primarily to hemolysis rather than disturbance of liver function. Dr. Culver also states that I have championed this viewpoint whereas the Thorndike school has favored the concept that excessive urobilinogenuria is related essentially to liver-function disturbance. He states, "There has been a running fight for a number of years between those two groups." I have been totally unaware of any such disagreement, since I have always taken the point of view that excesses of urobilinogen in the urine concerned liver-function disturbance, whether there was any histologic or other evidence of impairment or not. I have repeatedly pointed out that the amount of urinary urobilinogen is totally unreliable in the diagnosis of hemolytic jaundice, since many cases do not exhibit excesses and since marked excesses are often observed in patients who have no increase of blood destruction.

I would appreciate it if this correction could be called to the attention of your readers.

C. J. Watson, M.D.
Professor of Medicine
University of Minnesota Medical School
Minneapolis, Minnesota

BOOK REVIEWS

Bibliography of Medical Ex Libris Literature. By Samuel X. Radbill, M.D. With a foreword by Carlyle S. Baer. 8°, cloth, 40 pp., with illustrations. Los Angeles, California: Hilprand Press, 1951. $5.00.

This bibliography of bibliographies has long been needed because of the steadily growing interest in the bookplates of physicians, nurses and members of allied professions. Hitherto it has been necessary to consult the general reference works, or isolated lists for information on medical *ex libris.* There are fifteen reproductions of notable plates; the frontispiece is the plate of Dr. Radbill. This *de luxe* press book should be in all medical-history collections.

James F. Ballard

Für und wider die Sterilisierung aus eugenischer Indikation. By Dr. Hans Nachtsheim. 8°, paper, 64 pp., with 4 illustrations. Stuttgart: Georg Thieme, 1952. Kart. DM 5.70. (Distributed by Grune and Stratton, New York.)

This interesting paper on eugenic sterilization, which was presented to the Berliner medizinische Gesellschaft in December, 1951, is now printed for wider distribution. The arguments, for and against, are given in detail. The question in present-day Germany and in other countries is first discussed. It is noted that in the United States twenty-seven states have existing sterilization laws and that to January 1, 1951, a total of 51,282 operations have been performed. In three other states in which the laws have been repealed, the total was 951. In New York the law operated from 1912 to 1918, and it was negligible, since the total of operations was only 42. In Alabama, 1919–1935, and in Washington, 1909–1942, the total was 909 during these periods. In 1950 a total of 1526 sterilizations were performed, and it is interesting to note that three states, North Carolina, Georgia, and Virginia, had the highest percentages per 100,000 of population, respectively 7.26, 6.56 and 6.16. The German National Socialist law was directed against persons affected with congenital feeble-mindness, schizophrenia, circular insanity, hereditary epilepsy, Huntington's chorea, blindness, deafness and severe hereditary bodily deformities. Most of the text is devoted to a discussion of these conditions in relation to the procedure. The statistics quoted were obtained from publication number five of the Human Better-

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ment Association, New York, 1951. An appendix reproduces the Prussian law of 1932. A short but important bibliography concludes the text.

JAMES F. BALLARD

NOTICES

NEW ENGLAND SURGICAL SOCIETY

The annual meeting of the New England Surgical Society will be held at the Red Lion Inn, Stockbridge, Massachusetts, on September 19 and 20.

AMERICAN UROLOGICAL ASSOCIATION ESSAY AWARDS

The American Urological Association offers an annual award of $1,000 (first prize $500, second prize $300 and third prize $200) for essays on the result of some clinical or laboratory aspect of research in urology. Competition is limited to urologists who have been in such specific practice for not more than five years and to men in training to become urologists.

The essay winning first prize will appear on the program of the forthcoming meeting of the American Urological Association, to be held at the Hotel Jefferson, St. Louis, Missouri, May 11-14, 1953.

Further information may be obtained from the Executive Secretary, William P. Didusch, 1120 North Charles Street, Baltimore, Maryland. Essays must be in his hands before January 15, 1953.

NEW ENGLAND SOCIETY OF ANESTHESIOLOGISTS

The following meetings of the New England Society of Anesthesiologists will be held: October 3, Hanover, New Hampshire; November 18, Boston; February 6, Hartford, Connecticut; and April 3, Boston (annual meeting).

The November 18 meeting will be a joint meeting of the New England Society of Anesthesiologists and the Massachusetts Society of Anesthesiologists. The guest speaker will be Dr. Ivan S. Magill, of London, England.

SOCIETY MEETINGS AND CONFERENCES

SEPTEMBER 17. Phi Delta Epsilon Lecture. Page 338, issue of August 28.

SEPTEMBER 19. Combined Anesthesia Teaching Conferences of Boston. Page 304, issue of August 21.

SEPTEMBER 19 AND 20. New England Surgical Society. Notice above.

SEPTEMBER 23. Norfolk District Medical Society. Page 190, issue of July 31.

SEPTEMBER 24. Massachusetts Academy of General Practice. Fall meeting. Hotel Statler, Boston.

SEPTEMBER 26-28. Aero Medical Association. Page ix, issue of July 31.

OCTOBER 1. Essex North District Medical Society. Page 226, issue of August 7.

OCTOBER 1-3. Mississippi Valley Medical Society. Seventeenth Annual Meeting. Jefferson Hotel, St. Louis, Missouri. Page xiii, issue of August 21.

OCTOBER 1-3. American Medical Writers' Association. Page ix, issue of July 31.

OCTOBER 3, NOVEMBER 18, FEBRUARY 6 AND APRIL 3. New England Society of Anesthesiologists. Notice above.

OCTOBER 6-17. New York Academy of Medicine. Page xi, issue of July 24.

OCTOBER 8. New England Pediatric Society. Page 338, issue of August 28.

OCTOBER 14. Springfield Academy of Medicine. Page 190, issue of July 31.

OCTOBER 18-23. American Academy of Pediatrics. Page xi, issue of July 24.

OCTOBER 28-30. New England Postgraduate Assembly. Hotel Statler, Boston.

OCTOBER 29. New England Obstetrical and Gynecological Society. Annual Meeting. Hotel Somerset, Boston.

OCTOBER 30-NOVEMBER 1. National Association for Music Therapy. Page ix, issue of July 31.

OCTOBER 31 AND NOVEMBER 1. Eastern Section of American Trudeau Society. Page 190, issue of July 31.

NOVEMBER 2-7 AND 10-21. Courses in Laboratory Diagnosis of Tuberculosis. Page 354, issue of February 28.

NOVEMBER 9 AND 10. American Society for the Study of Arteriosclerosis. Page 78, issue of July 10.

NOVEMBER 11-14. American Society of Anesthesiologists, Inc. Third annual refresher course program. The Bellevue-Stratford, Philadelphia.

DECEMBER 7. American Academy of Dental Medicine. Hotel Statler, New York City. Page 338, issue of August 28.

JULY, 1953. International Congress on Medical Librarianship. Page 316, issue of February 21.

DISTRICT MEDICAL SOCIETIES

ESSEX SOUTH

OCTOBER 1. 6:45 p.m. Amesbury Country Club, Amesbury.

MIDDLESEX SOUTH

OCTOBER 29. 11:15 a.m. Mount Auburn Hospital, Cambridge.

NORFOLK

SEPTEMBER 23. Boston Medical Library.
OCTOBER 28.
NOVEMBER 25.
JANUARY 27, 1953.
FEBRUARY 24.
MARCH 24.

CALENDAR OF BOSTON DISTRICT FOR THE WEEK BEGINNING THURSDAY, SEPTEMBER 18

THURSDAY, SEPTEMBER 18

*9:00-10:00 a.m. Arthritis Grand Rounds. Robert Breck Brigham Hospital.
*11:00 a.m.-12:30 p.m. Hand Clinic (Physical Medicine and Rehabilitation Service). Boston City Hospital.
5:00 p.m. Case presentation and pathological discussion followed by a subject of special presentation. Joslin Amphitheater, New England Deaconess Hospital.
*5:00-6:00 p.m. Surgical Division Lecture. Mount Auburn Hospital, Cambridge.

FRIDAY, SEPTEMBER 19

*9:00 a.m.-12:00 m. Combined Medical and Surgical Staff Rounds. Peter Bent Brigham Hospital.
*10:00 a.m. Surgical Clinic. South End Health Unit, 57 East Concord Street.
10:30-11:15 a.m. Diabetes Lecture. Dr. Elliott Joslin. New England Deaconess Hospital.
*11:00 a.m.-12:00 m. Pediatric Conference. Mount Auburn Hospital, Cambridge.
*1:30 p.m. Fertility and Endocrine Clinic. Free Hospital for Women, Brookline.
7:00-9:00 p.m. Combined Anesthesia Teaching Conferences of Boston. Amphitheater, Evans Memorial, Massachusetts Memorial Hospitals, Eighth Floor, 65 East Newton Street, Boston.

SATURDAY, SEPTEMBER 20

*9:00 a.m. Proctology Clinic. Peter Bent Brigham Hospital.
*9:00 a.m. Alcoholism Clinic. Peter Bent Brigham Hospital.
*11:00 a.m.-12:00 m. Blood Clinic. Dr. William Dameshek. Stearns Auditorium, New England Center Hospital.

MONDAY, SEPTEMBER 22

*8:00-9:00 a.m. Combined Medical and Surgical Rounds for Diabetic Surgery Cases. New England Deaconess Hospital.
*8:30-9:30 a.m. Clinic by entire Surgical Staff and Anesthesia Staff. Cheever Amphitheater, Dowling Building, Boston City Hospital.
*12:15-1:15 p.m. Clinicopathological Conference. Main Amphitheater, Peter Bent Brigham Hospital.
*7:00-9:00 p.m. Anesthesia Teaching Conference. Stearns Auditorium, New England Center Hospital.

TUESDAY, SEPTEMBER 23

*9:00 a.m. Geriatrics Clinic. Peter Bent Brigham Hospital.
*12:00 m.-1:00 p.m. Pediatric Rounds. Burnham Memorial Hospital for Children, Massachusetts General Hospital.
*12:15-1:15 p.m. X-Ray Conference. Dr. Merrill Sosman. Main Amphitheater, Peter Bent Brigham Hospital.
*12:15-1:15 p.m. Clinicoroentgenological Conference. Peter Bent Brigham Hospital.
*5:00-6:00 p.m. Service Meeting followed by Clinical Conference (Medical, Surgical, Obstetrical). Faulkner Hospital.
8:00 p.m. Norfolk District Medical Society. John Ware Hall, Boston Medical Library.

WEDNESDAY, SEPTEMBER 24

Massachusetts Academy of General Practice. Fall Meeting. Hotel Statler, Boston.
*12:00 m. Boston State Hospital Psychiatric Seminar. Reception Building Auditorium, 591 Morton Street, Dorchester.
*12:00 m.-1:00 p.m. Medical Conference. (Children's Medical Center.) Jimmy Fund Building, 25 Binney Street.
12:30 p.m. Weekly Pathological Meeting. Joslin Amphitheater, New England Deaconess Hospital.
*4:00 p.m. Thoracic Conference. Harris Hall, New England Deaconess Hospital.
*4:00-5:30 p.m. Fracture Lecture. Boston City Hospital.
*6:00 p.m. Alcoholism Clinic. Peter Bent Brigham Hospital.

*Open to the medical profession.